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Quantification of Toxicological Effects of 1,2-Dichloroethane

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16. ABSTRACT

The Criteria and Standards Division, U.S. Environmental Protection Agency has prepared a section on the toxicological effects of 1,2-dichloroethane. This section may be used with the Health Assessment Document of 1,2-Dichloroethane which is attached. This document and toxicological effects section is an extensive review of the following topics:

- Occurrence of 1,2-dichloroethane in the environment
- 1,2-dichloroethane metabolism
- 1,2-dichloroethane toxicology
- 1,2-dichloroethane mutagenicity and carcinogenicity
- Human health risk assessment for 1,2-dichloroethane

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SEPTEMBER 1985

Critera and Standards Division
Office of Drinking Water
U.S. Enivironmental Protection Agency
Washington D.C.

The attached document entitled " Health Assessment for 1,2-Dichloroethane" can be consulted for more information on

- Sources in the Environment
- Environmental Levels and Exposure
- Biological Effects in Man and Experimental Animals

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VIII. Quantification of Toxicological Effects

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Adjusted Acceptable Daily Intake (ADI) for the chemical is determined. For ingestion data, this approach is illustrated as follows:

$$\text{Adjusted ADI} = \frac{(\text{NOAEL or MEL in mg/kg})(70\text{ kg})}{(\text{Uncertainty factor})(2\text{ liters/day})}$$

The 70 kg adult consuming 2 liters of water per day is used as the basis for the calculations. A "no-observed-effect-level" or a "minimal-effect-level" is determined from animal toxicity data or human effects data. This level is divided by an uncertainty factor because, for these numbers which are derived from animal studies, there is no universally acceptable quantitative method to extrapolate from animals to humans, and the possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human toxicity data, an uncertainty factor is used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxins. The guidelines set forth by the National Academy of Sciences (Drinking Water and Health, Vol. 1, 1977) are used in establishing uncertainty factors. These guidelines are as follows: an uncertainty factor of 10 is used if there exists valid experimental results on ingestion by humans, an uncertainty factor of 100 is used if there exists valid results on long-term feeding studies on experimental animals, and an uncertainty factor of 1000 is used if there exists scanty results on experimental animals.

In the quantification of carcinogenic effects, mathematical models are used to calculate the estimated excess cancer risks associated with the consumption of a chemical through the drinking water. EPA's Carcinogen Assessment Group have used the multistage model, which is linear at low doses and does not exhibit a threshold, to extrapolate from high dose animal studies to low doses of the chemical expected in the environment. This model estimates the upper bound (95% confidence limit) of the excess cancer rate that would be expected to occur at a specific exposure level for a 70 kg adult, consuming 2 liters of water per day, over a 70 year lifespan. Excess cancer rates can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There exists no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude. The multi-stage model often gives the highest risk estimate and thus would usually be the one most consistent with the conservative regulatory philosophy.

The scientific data base, which is used to support the setting of risk rate levels as well as other scientific endeavors, has an inherent uncertainty. This is due to the fact that it is not possible to measure a quantity with 100%

accuracy because the tools of scientific measurement by their very nature involve both systematic and random error. In addition, in many areas there is limited knowledge concerning the health effects of contaminants in drinking water, and in all areas uncertainty exists. When developing risk rate levels, several other areas of uncertainty exist such as the effect of age, sex, species and organ of the test animals used in the experiment, and the rate of exposure of the test animals or humans. The dose-response data is usually known at high levels of exposure, with no information being available at the levels of exposure for which a standard is being set. In most cases, data only exists for animals and thus uncertainty exists when the data is extrapolated to humans. Additional uncertainty exists when there is exposure to more than one contaminant due to the lack of information about possible synergistic and antagonistic effects.

Non-carcinogenic Effects

The toxic effects of 1,2-dichloroethane (1,2-DCE) in humans and other animals from both acute and longer-term exposures include central nervous system (CNS) depression, liver and kidney damage, gastrointestinal distress, adrenal and pulmonary effects and circulatory disturbances. The appearance and intensity of these effects are dependent upon dose and duration of exposure. Death following high level acute exposures usually results from respiratory or circulatory failure. Delayed fatalities usually are due to renal damage.

Fatty degeneration in the liver, heart and adrenal also have been observed.

No information is available on the existence of any subgroup of the human population which is likely to be more susceptible to the toxicity of 1,2-dichloroethane, nor is there any information on the nature of interaction between 1,2-DCE and other chemicals during multiple chemical exposure.

Reported minimum acute lethal doses in non-human mammals range from 600 to 2000 mg/kg (see Table VIII-1). The human may be more sensitive to the acute effects of this substance as there exists a case report describing the death of an adolescent male following ingestion of about 350 mg/kg of the solvent (Yodaiken and Babcock, 1973).

Some of the effects occurring after extended exposure in animals to 1,2-dichloroethane are described below in the section on Quantification of Non-carcinogenic Effects. Different effects were noted in rabbits exposed to 3000 ppm 1,2-DCE for 2 hr/day, 5 days/week for 90 days(Lioia and Elmino, 1959; Lioia, et al, 1959). These authors reported that the animals exhibited varying degrees of leukopenia and thrombocytopenia. In addition, there was frequent hypoplasia of the granuloblastic and erythroblastic parenchyma in the bone marrow. The cellular concentration of leukolipids was reduced, but no changes occurred in polysaccharides, peroxidase or RNA. The investigators suggested that 1,2-DCE might exert a direct poisoning effect on bone marrow.

Table VIII-1

Acute Lethal Doses of 1,2-Dichloroethane in Animals

Species	Category[a]	Dosage	Route
Mouse	LCL_o	5000 mg/m^3	Inhalation
	LDL_o	600 mg/kg	Oral
	LDL_o	380 mg/kg	Subcutaneous
	LDL_o	250 mg/kg	Intraperitoneal
Rat	LCL_o	1000 ppm/4 hr	Inhalation
	LDL_o	500 mg/kg	Subcutaneous
	LD_{50}	680 mg/kg	Oral
Guinea pig	LCL_o	1500 ppm/7 hr	Inhalation
	LDL_o	600 mg/kg	Intraperitoneal
Rabbit	LCL_o	3000 ppm/7 hr	Inhalation
	LDL_o	1200 mg/kg	Subcutaneous
	LD_{50}	860 mg/kg	Oral
Dog	LDL_o	2000 mg/kg	Oral
	LDL_o	175 mg/kg	Intravenous
Pig	LCL_o	3000 ppm/7 hr	Inhalation

[a] LCL_o:lowest published lethal concentration in air; LDL_o: lowest reported lethal dose by any route other than inhalation; LD_{50}: median lethal dose by any route other than inhalation.

Source: NIOSH, 1977, p.388

Quantification of Non-carcinogenic Effects

The only toxicological study published to date in which the test animals were exposed to 1,2-dichloroethane in their drinking water was reported by Lane, et al. (1982). The duration of dosing varied from 5 to 25 weeks, depending upon the particular protocol used. The authors conducted a multi-generation reproductive study which included screening for dominant lethal and teratogenic effects. Male and female ICR Swiss mice received the test substance at concentrations of 0, 0.03, 0.09 or 0.29 mg/l (0, 5, 15, or 50 mg/kg/day). Under the conditions of this study, there appeared to be no dose-dependent effects upon fertility, gestation, viability or lactation indices. Weight gain and pup survival were not affected adversely. No significant dominant lethal or teratogenic effects occurred in either of the two generations tested. The no-effect level of 50 mg/kg may not be the highest no-effect level since no higher doses were given. If one were to use the results of this study to derive an acceptable daily intake (ADI) for non-carcinogenic toxicity, it might be developed as follows:

$$\text{ADI:}\quad \frac{50\ \text{mg/kg/day} \times 100\%}{100 \times 10} = 0.05\ \text{mg/kg/day} \text{ (or 3.5 mg/day for a 70 kg adult)}$$

Where: 50 mg/kg/day = No-observed adverse effect level (NOAEL) for reproductive and teratogenic effects

70 kg = weight of protected individual

100% = percentage of dose absorbed

100 = uncertainty factor, appropriate for use with NOAEL from animal data, and no equivalent human data

10 = uncertainty factor, for less than lifetime exposure

The study by Alumot, et al. (1976), in which 250 or 500 ppm 1,2-dichloroethane was added to the feed of rats for up to two years, yielded no significant differences between treated and control animals. Even though the authors recommended an acceptable daily intake (ADI) of 25 mg/kg, inadequacies in the conduct and reporting of the study exist, rendering this experiment inappropriate for use in the derivation of an ADI.

Longer-term inhalation exposures (up to eight months) to 100 ppm 1,2-dichloroethane for 6 to 7 hours/day, 5 days/week in a variety of animal species yielded no adverse effects as measured by general appearance, behavior, mortality rates, growth rates, organ function and blood clinical chemistry in separate studies reported by Heppel, et al., 1946, Spencer, et al., 1951 and Hofmann, et al., 1971. Exposures at higher levels (400-500 ppm) for the same duration did result in increased mortality and some pathological findings, including pulmonary congestion, diffused myocarditis, slight to moderate fatty degeneration of the liver, kidney, adrenal and heart as well as increased prothrombin time. If one were to use the NOEL of 100 ppm identified in these three studies to derive an ADI for non-carcinogenic effects, the ADI might be developed as follows:

$$\text{ADI:}\quad \frac{405\ \text{mg/m}^3 \times 1\ \text{m}^3/\text{hr} \times 6\ \text{hr} \times 0.3 \times 5}{100 \times 10 \times 7} = \begin{array}{l}0.521\ \text{mg/day or}\\ 7.45\ \text{ug/kg/day}\\ \text{for a 70 kg adult}\end{array}$$

Where: $405\ mg/m^3$ = NOAEL of 100 ppm (1 ppm = $4.05\ mg/m^3$)

$1\ m^3/hr$ = respiratory rate of adult human (pulmonary rate/body weight ratio assumed to be the same for humans and test animals)

6 hours = exposure duration/day

5/7 = conversion of 5 day/week dosing to daily for 7 day/week

0.3 = fraction of test substance absorbed

100 = uncertainty factor, appropriate for use with NOAEL from animal data and no equivalent human data

10 = uncertainty factor, for less than lifetime exposure

From the data presented above, it is obvious that alterations in reproductive function do not represent the most sensitive end point of toxicity to this substance. The end-points identified in the inhalation studies are,for now, more appropriate indicators of 1,2-dichloroethane's noncarcinogenic toxicity. Therefore, the ADI derived from this series of studies will be used to develop an Adjusted ADI for noncarcinogenic effects for 1,2-dichloroethane. Assuming that there is no exposure to 1,2-dichloroethane from other sources, the Adjusted ADI would be derived thusly:

$$\frac{7.45\ \text{ug/kg/day} \times 70\ \text{kg} \times 100\%}{2\ \text{l}} = 0.260\ \text{mg/l}$$

Where: 7.45 ug/kg/day = ADI for 70 kg adult

70 kg = body weight of protected individual

100% = assumed percentage contribution to total exposure by drinking water

2 l = volume of drinking water imbibed/day by 70 kg adult

The Adjusted ADI is derived to reflect allowable daily exposure of a 70 kg adult drinking two liters of water per day, and whose sole source of exposure to 1,2-dichloroethane is via that drinking water.

Carcinogenic Effects

Near lifetime exposure to 1,2-dichloroethane has been shown to significantly increase tumor incidences at several sites in both rats and mice when administered by gavage, but not following inhalation exposures in these species (different strains) or thrice weekly intraperitoneal injections as measured by observing the incidence of lung adenomas in Strain A mice (NCI, 1978; Maltoni, et al., 1980; Theiss, et al., 1977). Negative results in the Strain A mouse system, however, are not considered to be sufficient evidence that a compound is not a carcinogen.

1,2-DCE at doses of 47 or 95 mg/kg/day was administered in corn oil by gavage five times weekly to 50 Osborne-Mendel rats of each sex per group for 78 weeks followed by an observation period of 23 weeks for males and 15 weeks for females. A statistically significant increase in the incidence of squamous cell carcinoma of the forestomach and hemangiosarcoma of the circulatory system was observed in male but not female rats ($P < 0.04$). The female rats had a significantly increased incidence of adenocarcinoma of the mammary glands ($P < 0.002$) (NCI, 1978).

In a complementary gavage study, 50 hybrid B6C3F1 mice of each sex per group were dosed five times weekly for 78 weeks with 195 or 97 mg/kg/day in corn oil for male mice and 299 or 149 mg/kg/day in corn oil for female mice. The mice were observed for 12 to 13 weeks following cessation of the treatment. A statistically significant increase in the incidence of mammary adenocarcinoma ($P < 0.04$) and endometrial stromal polyps or sarcomas ($P < 0.016$) was seen in the female mice; the incidence of alveolar/bronchiolar adenomas was increased in both sexes ($P < 0.028$) (NCI, 1978).

In an inhalation study, Swiss mice or Sprague-Dawley rats of each sex were exposed to 607.5, 202.5, 40.5, or 20.3 mg/m^3 of 1,2-DCE for 7 hours daily, 5 days per week for 78 weeks (Maltoni, et al., 1980). At the end of exposure period, the animals were allowed to live out their natural lives. In no case did the incidence of a particular type of tumor appear to be dose-related. In this interim report, the authors concluded that 1,2-DCE was not carcinogenic under the conditions of their experiment.

Several explanations have been proposed to reconcile the differences in the results of the gavage and inhalation studies. These are presented in some detail in Chapter V. On the basis of the results of the NCI bioassay, IARC (1979) concluded that there was sufficient evidence for 1,2-dichloroethane's carcinogenicity in test animals. For compounds classified as having sufficient evidence of carcinogenicity in animals, but lacking adequate data in humans (which would be the case for 1,2-dichloroethane), IARC states that "it is reasonable, for practical purposes, to regard such chemicals as if they presented a carcinogenic risk to humans" (IARC, 1979).

1,2-Dichloroethane was shown to be carcinogenic by the oral route, the same route by which individuals would be exposed to 1,2-dichloroethane when it is present in their drinking water. Therefore, one must determine whether or not a carcinogenic risk exists and, if so, estimate the magnitude of that risk to individuals drinking water which contains measurable levels of this substance.

1,2-DCE has been studied in a variety of short-term test systems which evaluate the mutagenic potential of the compound and/or its potential for interaction with DNA. The results of these studies are summarized in Table V-21. Positive results in certain of these test systems are considered to be predictive of carcinogenic potential.

When considering the body of data as a whole, it becomes evident that 1,2-dichloroethane probably exerts its carcinogenicity primarily via genotoxic mechanism(s). On the assumption that this is so, one must now try to estimate the risk to humans that exposure to this substance in the drinking water would pose. Scientists have not been able to demonstrate a threshold established for this mechanism of action. Therefore, exposure to any amount of this type of toxicant obligates some measure of risk. Since we do not have experimental results for effects seen at low doses of exposure, we must mathematically extrapolate from the results obtained at higher doses to project what would be expected at the lower doses.

Quantification of Carcinogenic Effects

Using methodology described in detail elsewhere, the EPA's Carcinogen Assessment Group (CAG) has calculated estimated incremental excess cancer risks associated with exposure to 1,2-dichloroethane in ambient water, extrapolating from data obtained in the NTP Bioassay in male rats with this compound (increased incidence of hemangiosarcomas) (U.S. EPA, 1980; NCI, 1978). CAG employed a linear, non-threshold multistage model to estimate the upper bound 95% confidence limit of the excess cancer rate that would occur at a specific exposure level for a 70 kg adult, ingesting 2 liters of water and 6.5 g of fish and seafood/day ("fish factor"), every day over a 70-year lifespan.

The National Academy of Sciences (NAS, 1977;1980) and EPA's CAG (Anderson, 1983) have estimated upper 95% confidence limit excess cancer risk rates associated with consumption of 1,2-dichloroethane via drinking water alone. Each group used the linearized, non-threshold multistage model. NAS derived its estimates using data from the NCI bioassay showing an increased incidence of squamous cell carcinomas of the forestomach in male rats, mammary tumors in female rats and mice, endometrial tumors in female mice and lung adenomas in mice of both sexes. At the request of the Office of Drinking Water, CAG generated estimates based upon 1) mammary adenocarcinomas in female mice, 2) mammary adenocarcinomas in female rats, 3) squamous cell carcinomas in the forestomach of male rats, and 4) a combined risk incorporating the above three as well as the hemangiosarcomas in male rats. It is this combined risk (4)) that the ODW has chosen to represent CAG's extrapolation for drinking water.

In all three instances, a range of 1,2-dichloroethane concentrations were computed that would be estimated to increase the risk by one excess cancer per million (10^6), per one hundred thousand (10^5) and per ten thousand (10^4) people over a 70-year lifetime assuming daily consumption of 2 liters of water by a 70 kg adult at the stated exposure level. The ranges of concentrations are summarized in Table VIII-2.

Table VIII-2

Drinking Water Concentrations and Estimated Excess Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)[a]		
	CAG[b]	CAG[c]	NAS[d]
10^{-4}	94	59.9	70
10^{-5}	9.4	6.0	7
10^{-6}	0.94	0.6	0.7
0	0.00	0.00	0.00

[a] Assumes the consumption of two liters of water per day by 70 kg adult over a lifetime; number represents 95% upper bound confidence limit

[b] (U.S. EPA, 1980)

[c] (Anderson, 1983)

[d] (NAS, 1977;1980)

United States
Environmental Protection
Agency

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Washington DC 20460

EPA-600/8-84-006A
April 1984
External Review Draft

Research and Development

EPA

Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride)

Review
Draft

(Do Not
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Part 1 of 2

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF WATER

Susan

MAY 15 1984

MEMORANDUM

SUBJECT: HEB Review of OHEA Health Assessment Document on 1,2-Dichloroethane- April, 1984 External Review Draft

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FROM: Penelope A. Fenner-Crisp, Ph.D.
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THRU: William L. Lappenbusch, Ph.D., Chief
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The April 1984 External Review Draft of the OHEA Health Assessment Document (HAD) on 1,2-Dichloroethane (Ethylene Dichloride) has been reviewed solely for its consistency with the Office of Drinking Water's Health Effects Criteria Document. This comparison was made only with respect to the conclusions reached concerning the results of experiments performed to evaluate the non-carcinogenic and carcinogenic properties of the substance.

For the non-carcinogenic effects, the qualitative judgment is the same in both documents. A NOAEL of 100 ppm and an effect level of 400 ppm by inhalation was identified in both cases. The data are inadequate for identifying NOAELs or effect levels for the most sensitive end-point(s) of toxicity following oral exposure. The OHEA HAD did not develop a quantitative assessment for the non-carcinogenic effects of the compound.

Both documents concluded that 1,2-dichloroethane is a weak mutagen in several test systems without metabolic activation and a more potent mutagen in many test systems following metabolic activation. The ODW document uses this information to suggest that 1,2-dichloroethane probably exerts its carcinogenic effect via a genetic mechanism. The OHEA HAD makes no statement on this.

There is consensus on the carcinogenic potential of 1,2-dichloroethane. Both of the NCI gavage bioassays (rat and mouse) showed that the compound induced a significant increase in tumor incidence at several sites in each species. The Carcinogenic Assessment Group derived an upper bound estimate of cancer risk if exposure is via drinking water based upon the increased number of hemangiosarcomas in male rats, concluding that the risk from 1 ug/L equals 2×10^{-6}. This would equate to a concentration of about 0.5-0.6 ug/L for a risk of 1 in a million. This estimate is consistent with that relayed to ODW in a memo from Elizabeth Anderson in March, 1983. ODW derived an estimate of excess cancer risk based upon the combined data showing an increase in tumors in the 1) mammary gland of female rats and mice (adenocarcinomas), 2) forestomach of male rats (squamous cell carcinomas), and 3) hemangiosarcomas in male rats. These two sets of risk estimates, along with that performed by the National Academy of Sciences are duly noted in the QTE section of the ODW document. They all are essentially identical.

(Do Not
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April 1984
External Review Draft

Health Assessment Document for 1, 2, - Dichloroethane (Ethylene Dichloride)

Part 1 of 2

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DISCLAIMER

This report is an external draft for review purposes only and does not constitute Agency Policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a "source document" for EPA use. The health assessment document was originally developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulation of ethylene dichloride as a hazardous air pollutant. However, the scope of this document has since been expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses are placed in perspective with observed environmental levels.

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The EPA's Office of Health and Environmental Assessment (OHEA) is responsible for the preparation of this health assessment document. The OHEA Environmental Criteria and Assessment Office (ECAO-RTP) had overall responsibility for coordination and direction of the document (Dr. Robert M. Bruce, Project Manager). The chapters addressing physical and chemical properties, sampling and analysis and toxic effects were either rewritten or revised by Syracuse Research Corporation. The pharmacokinetics chapter was written by Dr. I.W.F. Davidson of the Bowman Gray School of Medicine, Wake Forest University. The air quality chapters addressing sources, emissions and ambient concentrations were originally written by Syracuse Research Corporation and revised by Radian Corporation under a contract with the Office of Air Quality Planning and Standards.

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The OHEA Carcinogen Assessment Group (CAG) was responsible for preparation of the sections on carcinogenicity. Participating members of the CAG are listed below (principal authors of present carcinogenicity materials are designated by an asterisk (*).

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The OHEA Reproductive Effects Assessment Group (REAG) was responsible for the preparation of sections on mutagenicity, teratogenicity and reproductive effects. Participating members of REAG are listed below (principal authors of present sections are indicated by an asterisk (*). The Environmental Mutagen Information Center (EMIC), in Oak Ridge, TN, identified literature bearing on the mutagenicity of EDC.

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1. SUMMARY AND CONCLUSIONS

Ethylene dichoride (EDC) is a clear, colorless, volatile liquid with a pleasant odor. EDC has a molecular weight of 98.96 amu, a boiling point of 83.7°C and a vapor pressure of 64 torr at 20°C. Unlike more highly chlorinated hydrocarbons, EDC has a flashpoint (17°C closed cup), an autoignition temperature (413°C) and explosive limits (6.2-15.6% by volume in air). It has a water solubility of 8820 mg/ℓ and a log octanol/water partition coefficient of 1.48.

EDC is analyzed best by gas chromatography using either an electron capture or halogen specific (microcoulometric or electrolytic conductivity) detector. Alternatively, a gas chromatograph/mass spectrometer may be used. EPA methods 502.1, 601, 624 and 8010 detail the analysis of EDC from water, wastewater and solid samples. Variations in these methods provide for analysis of EDC in biological media (e.g., blood, urine and tissue). EDC in air is analyzed by condensing the volatiles in a previously collected air sample in a GC column, followed by temperature programming the column.

EDC is produced commercially by the direct chlorination or oxychlorination of ethylene. Most of the production capacity, which exceeds nine million metric tons annually, is located in Texas and Louisiana. Roughly 90% of the production is captively consumed by the producers. Production during 1980, 1981 and 1982 totalled 5.037, 4.523 and 3.455 million metric tons, respectively. A major portion (84%) of the United States EDC production is consumed to make vinyl chloride monomer. It is also used to make chlorinated solvents, vinylidene chloride and ethyleneamines.

The major source of EDC emissions to the environment are from vent gas streams during the manufacture of EDC and its derivatives. Significant amounts are also emitted to the environment from dispersive uses in gasoline, paints and cleaning agents. In 1979, an estimated 6696 metric tons of EDC were released to the atmosphere from EDC and derivative production, while 4944 metric tons were released from dispersive uses (Seufert et al., 1980).

Based on available kinetic data and average tropospheric hydroxyl free radical concentration, the half-life of EDC, the most likely removal mechanism for EDC from the atmosphere, has been estimated to range from 36-127 days. Due to different factors that may cause variations in •OH concentrations in the troposphere, the persistence of EDC could vary somewhat from the estimated value. Chloroacetyl chloride is probably the principal product resulting from the reaction of EDC with •OH radicals.

EDC is not expected to play a significant role in stratospheric ozone destruction reactions due to its relatively short tropospheric half-life. However, chloroacetyl chloride may have sufficient stability to diffuse to the stratosphere and may participate in UV reactions, producing chlorine atoms.

In the aquatic environment, volatilization appears to be the most significant removal mechanism. The half-life for this process has been estimated to be ≈4 hours.

From the little information that is available regarding the fate of EDC in soil, it can be surmised that both volatilization from and leaching through soil may be two significant removal mechanisms for EDC.

The highest atmospheric concentrations that have been monitored for EDC have been detected near production and use facilities. Mean levels as high as 27.5 ppb have been monitored near production-use facilities in Lake Charles, LA (Elfers, 1979). However, atmospheric exposure appears to vary greatly from one location to another. The available monitoring data, which includes levels detected in general ambient urban areas, indicate that most locations have concentrations of $\leq$0.5 ppb. The data are not sufficient to determine regional variations in exposure levels. Using Federal Reporting Data System data, Letkiewicz et al. (1982) have projected that EDC levels in all groundwater and surface water systems in the United States fall below 10 μg/ℓ, and that most are <1.0 μg/ℓ. No data are available indicating the presence of EDC in finished foods.

Pharmacokinetic studies with animals indicate that EDC is rapidly absorbed following oral and inhalation exposure. Dermal absorption is negligible in most vapor exposure situations, although absorption by this route may be significant with direct liquid contact. Tissue distribution of EDC is consistent with its lipophilic nature, and the chemical crosses the blood/brain and placental barriers and distributes into breast milk. Up to 90% of low oral or inhalation doses are metabolized by rats and mice, with biotransformation occurring by multiple pathways; EDC is metabolized to 2-chloroacetaldehyde, S-(2-chloroethyl) glutathione and other putative reactive metabolites capable of covalent binding to cellular macromolecules, as well as nonreactive glutathione conjugates. Elimination of unmetabolized EDC occurs almost exclusively via the lungs, is rapid and is consistent with a two-compartment system and Michaelis-Menten kinetics. Significant bioaccumulation is not expected to occur.

The effects of acute inhalation exposure to EDC are similar in humans and animals. Immediate symptoms of toxicity are CNS depression and irritation of the respiratory tract and eyes. Death was usually ascribed to respiratory and circulatory failure, and pathologic examinations typically revealed congestion, degeneration, necrosis and hemorrhagic lesions of most internal organs (e.g., liver, kidneys, spleen, lungs, respiratory tract, gastrointestinal tract).

Limited data, primarily from the foreign literature, suggest that typical symptoms and signs of acute toxicity may develop in humans with repeated occupational exposure to higher concentrations (>60 ppm) of EDC vapor. Subtle neurological effects (e.g., fatigue, irritability, sleeplessness) may be more prevalent than overt symptoms of CNS toxicity at lower concentrations. Studies with multiple species of animals have shown that subchronic or chronic exposure to EDC at vapor concentrations of $\leq$ 100 ppm did not produce treatment-related adverse effects on survival, growth, hematology, clinical chemistry, organ weight or histology. Toxic effects were apparent at higher concentrations and were exposure-related; exposure to 400-500 ppm produced high mortality and histopathological alterations in rodents within a few exposures.

Limited data indicate that the toxic response to acute oral exposure is similar to that of inhalation exposure in humans and animals. Subchronic/chronic oral administration of EDC at daily dosages of ≈200 mg/kg and higher caused decreased growth rate and mortality in mice, which may have been tumor-related. Chronic oral administration of lower dosages of EDC (≈34 mg/kg/day) to rats produced mortality that appeared to be due to non-neoplastic lesions including bronchiopneumonia and endocardial thrombosis.

The available evidence suggests that EDC does not adversely affect the reproductive or development process in laboratory animals except at maternally toxic levels. Additional studies are needed, however, particularly with humans, to conclusively establish that EDC is not a teratogen and does not cause adverse reproductive effects.

Positive responses in different test systems representing a wide range of organisms indicate that EDC is a weak direct-acting mutagen capable of causing gene mutations. Several of its putative metabolites, thought to be formed in rats and mice, are judged to be more potent mutagens than EDC. EDC has not been adequately tested for its ability to cause chromosomal aberrations or heritable effects. Further testing is needed to assess its ability to cause these effects.

EDC was shown to be carcinogenic in a lifetime gavage bioassay that was conducted by the National Cancer Institute, producing tumors in both rats (forestomach carcinomas, cirulatory system hemangiosarcomas, subcutaneous fibromas, mammary gland adenocarcinomas) and mice (hepatocellular carcinomas, alveolar/bronchiolar adenomas, mammary carcinomas, endometrial tumors). EDC did not produce a statistically significant increase in the incidence of lung adenomas in strain A mice when administered intraperitoneally. However, benign lung tumors (but not skin tumors) were induced in mice when applied to the skin. No statistically significant increases in tumors occurred in rats or mice following lifetime inhalation exposure. No case reports or epidemiologic studies concerning EDC were avilable in the published literature for analysis.

From a weight-of-evidence approach, the direct and supporting evidence for carcinogenicity includes: 1) positive findings in one oral rat study and one oral mouse study, and supportive evidence in two other mouse studies; and 2) findings that EDC is weakly mutagenic, and that certain metabolites show evidence of even greater mutagenic potency. By using the International Agency for Research on Cancer (IARC) classification scheme, the level of animal evidence, combined with the nonexistence of human data, would constitute sufficient animal evidence that EDC is a probable human carcinogen, the overall IARC ranking being Group 2B. Using the animal data and a linear multistage extrapolation model, the upper-bound estimate of potency for EDC is $q_1^* = 7 \times 10^{-2}$ mg/kg/day calculated on the basis of hemangiosarcomas in rats. The upper-bound estimate of the cancer risk from ingesting water contaminated with 1 µg/ℓ of EDC is 2×10^{-6}. The potency index for EDC lies in the fourth quartile among 53 suspect carcinogens evaluated by the Carcinogen Assessment Group. These potency and risk values are upper-bound estimates; that is to say that the true values, while not identifiable, would not likely exceed the upper-bound, and may be lower.

2. INTRODUCTION

EPA's Office of Research and Development has prepared this health assessment to serve as a "source document" for Agency use. This health assessment was originally developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulations of ethylene dichloride under Section 112 of the Clean Air Act. However, based on the expressed interest of other agency offices, the scope of this document was expanded to address ethylene dichloride in relation to sectors of the environment outside of air. It is fully expected that this document will serve the information needs of many government agencies and private groups that may be involved in decision-making activities related to ethylene dichloride.

In the development of the assessment document, existing scientific literature has been surveyed in detail. Key studies have been evaluated and summary and conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified.

The document considers all sources of ethylene dichloride in the environment, the likelihood for its exposure to humans, and the possible effect on man and lower organisms from absorption. The information found in the document is integrated into a format designed as the basis for performing risk assessments. When appropriate, the authors of the document have attempted to identify gaps in current knowledge that limit risk evaluation capabilities.

3. PHYSICAL AND CHEMICAL PROPERTIES

3.1. NAME

Ethylene dichloride (EDC) is the common name for 1,2-dichloroethane. It is also commonly referred to as ethylene chloride and S-dichloroethane (Archer, 1979).

3.2. CAS REGISTRY, RTECS, AND STORET NUMBERS

CAS Registry: 107-06-2

RTECS: KI05250000

STORET: 34531

3.3. DESCRIPTION

Ethylene dichloride is a clear, colorless, volatile liquid with a pleasant odor, and is stable at ordinary temperatures (Archer, 1979).

3.4. STRUCTURE

$ClCH_2CH_2Cl$

3.5. PHYSICAL PROPERTIES OF PURE ETHYLENE DICHLORIDE

The physical properties of pure ethylene dichloride were taken from Archer (1979) and Weast (1980), unless otherwise stated.

Molecular weight:	98.96
Melting point:	-35.3°C
Boiling point:	83.7°C
Density at 20°C:	1.2529 g/ml
Viscosity:	1.4451 m Pa S (cP)
Flashpoint:	
Closed cup	17°C
Open cup	21°C
Explosive limits in air at 25°C:	6.2-15.6% by volume

Autoignition temperature in air: 413°C

Vapor pressure:

°C	kPa	Torr
10	5.3	40
20	8.5	64
30	13.3	100

Solubility in water: 0.0891 M (Valvani et al., 1981)
8,820 mg/ℓ

Log Octanol/Water Partition Coefficient: 1.48 (Valvani et al., 1981)

Henry's Law Constant atm m^3 mol^{-1}: 9.14×10^{-4} (Mabey et al., 1981)

Blood/Air Partition Coefficient (37°C): 19.5 ± 0.5 (Sato and Nakajima, 1979)

4. SAMPLING AND ANALYSIS OF ETHYLENE DICHLORIDE

4.1. SAMPLING

Taking environmental samples representative of the area in question is a complex task beyond the scope of this document. A number of documents either devoted exclusively to sampling or containing considerable information relating to the subject are listed below and should be consulted prior to initiating environmental sampling. For air, Singh et al. (1979, 1983), Pellizzari (1978), and Pellizzari et al. (1979) have detailed sampling methodologies that describe and/or show equipment and strategies. Water and wastewater sampling is described by U.S. EPA (1982a) and solids sampling by U.S. EPA (1982b).

4.2. ANALYSIS

4.2.1. Ethylene Dichloride in Air. Ethylene dichloride in air can be analyzed by a number of methods; however, the method of Singh et al. (1980) appears to be substantially free of artifact problems and completely quantitative. In this method, an air sample in a stainless steel canister at 32 psig is connected to a preconcentration trap consisting of a 4" x 1/16" ID stainless steel tube containing glass beads, glass wool, or 3% SE-30 on acid washed 100/120 mesh Chromosorb W. The sampling line and trap, maintained at 90°C, are flushed with air from the canister; then the trap is immersed in liquid O_2 and air is passed through the trap, the initial and final pressure being noted (usually between 30 and 20 psig) on a high-precision pressure gauge. The ideal gas law can be used to estimate the volume of air passed through the trap. The contents of the trap are desorbed onto a chromatography column by backflushing it with an inert gas while holding the trap at boiling water temperature. An Ascarite trap may be inserted before the chromatography column to remove water. Suitable columns include 10% SP-1000 on Supelcoport (100/120 mesh, 15' x 1/8" stainless steel) and 0.2% CW-

1500 on Carbopack C (80/100 mesh, 10' x 1/8" Ni). Both columns can be operated at 45°C with a carrier gas flow of 25 mℓ/minute on the former column and 40 mℓ/minute on the latter. An electron capture detector operating at 330°C was found to be optimum. It should be noted that the above authors found Tenax to be unsuitable for air analyses because of the presence of artifacts in the spectrum from oxidation of the Tenax monomer. In addition, when Tenax is used as a sorbent, safe sampling volumes (i.e., that volume of air which, if sampled over a variety of circumstances, will not cause significant breakthrough) should be adhered to. Brown and Purnell (1979) determined the safe volume for ethylene dichloride per gram Tenax to be 27 ℓ (flow rate 5-600 mℓ/minute; ethylene dichloride conc. <250 mg/m^3; temp. up to 20°C) with a safe desorption temperature of 90°C.

The detection limits of this method were not specified and are dependent on the volume of air sampled. Analyses as low as 33 ppt have been reported using this method (Singh et al., 1980).

4.2.2. Ethylene Dichloride in Water. Ethylene dichloride in water can be analyzed by the purge-and-trap method (Method 502.1) as recommended by the Environmental Monitoring and Support Laboratory of the U.S. EPA (1981). In this method, an inert gas is bubbled through 5 mℓ of water at a rate of 40 mℓ/minute for 11 minutes, allowing the purgable organic compounds to partition into the gas. The gas is passed through a column containing 3% OV-1 on Chromosorb W, Tenax GC silica gel, and coconut charcoal at 22°C, which traps most of the organics removed from the water. The adsorption column is then heated rapidly to 180°C and backflushed with helium (20-60 mℓ/minute, 4 minutes) to desorb the trapped organics. The effluent of the column is passed into an analytical gas chromatography column packed with 1% SP-1000 on Carbopack-B (60/80 mesh, 8' x 0.1" ID) maintained at 40°C. The column is then temperature programmed starting at 45°C for 3 minutes and increasing at 8°C/minute until 220°C is reached; it is then held there for 15 minutes or until all compounds have eluted. A halogen-specific detector (or GC-MS) having a sensitivity of 0.10 µg/ℓ with a relative standard deviation of <10% must be used. This method is similar to EPA method 601,624 for use with wastewater (U.S. EPA, 1982c).

4.2.3. Ethylene Dichloride in Solid Samples. Ethylene dichloride in solid samples may be analyzed by EPA method 8010 "Halogenated Volatile Organics" (U.S. EPA, 1982b). With this method, a portion of the sample is dispersed in polyethylene glycol or methanol. The dispersion is then mixed with water and purged in a manner identical to the analysis of EDC in water. The trap contains 3% OV-1 on Chromosorb W (60/80 mesh), Tenax GC (60/80 mesh), Grade 15 silica gel (35/60 mesh), and activated coconut charcoal (6/10 mesh); desorption is performed at 180°C for 4 minutes with a gas flow of 20 to 60 mℓ/minute. Gas chromotographic conditions are identical to the analysis of ethylene dichloride in water.

4.2.4. Ethylene Dichloride in Blood. Ethylene dichloride in blood can be analyzed by using a modified purge-and-trap method (Pellizzari et al., 1979). This method involves diluting an aliquot of whole blood (with anticoagulant) to ≈50 mℓ with prepurged, distilled water. The mixture is placed in a 100 mℓ 3-neck round bottom flask along with a teflon-lined magnetic stirring bar. The necks of the flask are equipped with a helium inlet, a Tenax trap, and a thermometer. The Tenax trap is a 10 cm x 1.5 cm ID glass tube containing pre-extracted (soxhlet, methanol, 24 hrs) and conditioned (270°C, 30 mℓ/minute helium flow, 20 minutes) 35/60 mesh Tenax (≈1.6 g, 6 cm). The sample is then heated to 50°C and purged with a helium flow rate of 25 mℓ/min for 90 minutes. Analysis can be performed as indicated in Section 4.2.2.

4.2.5. Ethylene Dichloride in Urine. Ethylene dichloride in urine can be analyzed by using an apparatus identical to the one described in Section 4.2.4, using 25 mℓ of urine, diluted to 50 mℓ, instead of blood.

4.2.6. Ethylene Dichloride in Tissue. Ethylene dichloride in tissue can be analyzed by using an apparatus identical to the one described in Section 4.2.4, using 5 g of tissue, diluted to 50 mℓ, instead of blood and macerated in an ice bath. The purge time is reduced to 30 minutes.

5. SOURCES IN THE ENVIRONMENT

5.1. PRODUCTION PROCESSES

Two commercial processes account for virtually all of the EDC produced currently. One is the direct chlorination of ethylene with chlorine. The other is an oxychlorination process in which ethylene, hydrogen chloride and oxygen are reacted to form EDC. Currently, most production centers around large manufacturing plants employing a balanced combination of both of these two processes. Over 80% of the EDC produced is used to make vinyl chloride monomer via dehydrohalogenation of EDC. Most EDC producers have nearby vinyl chloride production facilities. The balanced plants use the hydrogen chloride recovered when the EDC is dehydrohalogenated to vinyl chloride as feed to the oxychlorination reactor. This requires roughly a 50-50 split between direct chlorination and oxychlorination for a completely balanced operation assuming all EDC is cycled to the vinyl chloride facilities. In this manner, there will be no net production of hydrogen chloride. As of 1974, ≈58% of the total EDC production capacity was based upon direct chlorination and ≈42% was based upon oxychlorination (Pervier et al, 1974). Current capacities are judged to be roughly the same.

In the direct clorination process, EDC is produced by the catalytic vapor-or liquid-phase chlorination of ethylene as follows (Archer, 1979):

$$CH_2 = CH_2 + Cl_2 \text{ (5\% air)} \xrightarrow[40\text{-}50^\circ C]{FeCl_3} ClCH_2CH_2Cl$$

Most liquid-phase processes use ferric chloride as the catalyst. The chlorination is carried out at 40-50°C with 5% air added to prevent substitution chlorination of the product.

The oxychlorination process is usually incorporated into an integrated vinyl chloride plant in which hydrogen chloride (which is recovered from cracking the EDC to vinyl chloride) is recycled to an oxychlorination unit (Archer, 1979). The hydrogen chloride by-product is used as the chlorine source in the chlorination of ethylene in the presence of oxygen and copper chloride catalyst as follows:

$$2CH_2 = CH_2 + 4HCl + O_2 \xrightarrow[270°C]{CuCl_2} 2ClCH_2CH_2Cl + H_2O$$

5.2. ETHYLENE DICHLORIDE PRODUCERS

The producers of EDC in the U.S. are listed in Table 5-1 along with their respective production capacities. As can be noted from Table 5-1, most of the production capacity is located in Texas and Louisiana. These production facilities also captively consume the major portion of the EDC produced, as in the manufacture of vinyl chloride and, to a much lesser extent, in the manufacture of vinylidene chloride and various chlorinated solvents. From Table 5-2, it can be noted that only ≈10% of the EDC production has been sold on the open market in most recent years.

5.3. ETHYLENE DICHLORIDE PRODUCTION AND TRENDS

U.S. production volumes and sales of EDC are listed in Table 5-2. Blackford (1974) and the U.S. International Trade Commission (1974) have stated that the production volumes as listed may be somewhat smaller than the actual production because some EDC may be produced, but not separated or accurately measured (and therefore not reported) by some producers. Blackford (1974) has estimated actual productions on the order of 10% higher than the reported productions.

The demand for EDC for the years 1982 and 1983 has been estimated to be 4.127 and 4.716 million metric tons, respectively, while the demand for the year 1987 is expected to be 5.487 million metric tons (CMR, 1983). Production of EDC in 1982 was sharply lower than in preceding years (see Table 5-2). This was largely due to a recession in the vinyl chloride market and a decision of

TABLE 5-1

Major Manufacturers of Ethylene Dichloride[a]

Manufacture	Plant Sites	Annual Capacity (Millions of Metric Tons)
Atlantic Richfield (ARCO)	Port Arthur, TX	0.200
Borden, Inc.	Geismar, LA	0.230
Dow Chemical USA	Freeport, TX	0.725
	Oyster Creek, TX	0.500
	Plaquemine, LA	0.840
E.I. duPont (Conoco)	Lake Charles, LA	0.525
Ethyl Corp.	Baton Rouge, LA	0.320
	Pasadena, TX	0.110
Formosa Plastics Corp.	Baton Rouge, LA	0.240
	Point Comfort, TX	0.385
Georgia-Pacific Corp.	Plaquemine, LA	0.735
B.F. Goodrich Co.	Deer Park, Tx[b]	0.110
	La Porte, TX	0.720
	Calvert City, KY	0.450
	Convent, LA	0.360
PPG Industries	Lake Charles, LA	1.230
Shell Chem. Co.	Deer Park, TX	0.620
	Norco, LA[c]	0.540
Union Carbide Corp.	Taft, LA[d]	0.070
	Texas City, TX[d]	0.070
Vulcan Materials Co.	Geismar, LA	0.160
	Total	9.140

Note: Capacities are flexible depending on finishing capacities for vinyl chloride and chlorinated solvents.

[a] SRI, 1983; CMR, 1983

[b] Operated under a toll agreement with Diamond Shamrock Corp.

[c] Closed for an indefinite time period because of the temporary closing of Shell's vinyl chloride monomer plant located there.

[d] Captive use only.

TABLE 5-2

U.S. Production and Sales of Ethylene Dichloride[a]

	Millions of Metric Tons	
Year	Production[b]	Sales
1982	3.455	0.640
1981	4.523	0.401
1980	5.037	0.510
1979	5.349	0.633
1978	4.989	0.469
1977	4.987	0.692
1976	3.647	0.617
1975	3.617	0.345
1974	4.156	0.596
1973	4.214	0.613
1972	3.541	0.656
1971	3.428	0.595
1970	3.383	0.596
1965	1.113	0.140
1960	0.575	0.198
1950	0.138	0.021

[a] USITC, USTC, 1952-1982

[b] Production totals may be understated in some years because some ethylene dichloride is produced but not separated or accurately measured (and therefore not reported) by some producers.

producers to use their EDC inventories during the winter of 1982 (Chemical and Engineering News, 1982, 1983). Production of EDC is expected to rebound during 1983. Historically, the demand for EDC grew at a rate of ≈1% per year during the period from 1973-1982. Demand is anticipated to grow at a rate of 4% per year through 1987 (CMR, 1983).

5.4. ETHYLENE DICHLORIDE USES

A major portion (84%) of U.S. EDC production is converted to vinyl chloride monomer. The major uses of EDC for the years 1983, 1980, 1977 and 1974 are given in Table 5-3. Consumption of EDC for specific end-uses is given in Table 5-4.

In addition to vinyl chloride, EDC is used as a starting material in the production of chlorinated solvents such as 1,1,1-trichloroethane, trichloroethylene and perchloroethylene and as intermediate in the production of ethyleneamines and vinylidene chloride (Archer, 1979; Blackford, 1974). Table 5-5 lists the users of EDC for these purposes. In general, these users are also producers of EDC.

EDC is used as an additive (lead scavenger) in tetraethyllead antiknock mixtures for gasolines. Scavenging agents are used in gasolines to transform the combustion products of lead alkyls to forms that are more likely to be vaporized from the engine surfaces. The most important lead scavengers used for this purpose are EDC and ethylene dibromide (McCormack et al., 1981; Blackford, 1974). The sale of tetraalkyllead compounds is always in admixture with EDC and/or ethylene dibromide. Conventional motor-mix formulations contain 1 mol of EDC and 1/2 mol of ethylene dibromide per mol of tetraethyllead (McCormack et al., 1981). This use of EDC is expected to decline in future years due to EPA regulations concerning the use of leaded gasolines. CMR (1982) projects that the demand for lead in gasoline will decrease at a rate of 11% per year (average) through 1986.

TABLE 5-3

Ethylene Dichloride Uses[a]

Use	Percent of Total			
	1983	1980	1977	1974
Vinyl chloride monomer	84	84	80	78
Chlorinated solvents	4	7	10	8
Vinylidene chloride	2	2	--	--
Exports	9	5	--	--
Lead scavenger	--	--	3	3
Amines	--	--	--	2
Miscellaneous	1[b]	2[b]	7[c]	9[c]

[a] CMR, 1974, 1977, 1980, 1983

[b] includes lead scavenger

[c] includes exports

TABLE 5-4

Consumption of Ethylene Dichloride in 1979 and 1974[a]

	Consumption (Thousands of Metric Tons)			
	1979	%	1974	%
Vinyl chloride monomer	4420	85.0	3894.2	81.0
1,1,1-Trichloroethane	--	--	153.3	3.2
Trichloroethylene	89.4	1.7	132.8	2.8
Perchloroethylene	--	--	124.7	2.6
Vinylidene chloride	118.7	2.3	97.0	2.0
Ethyleneamines	168.1	3.2	131.5	2.7
Lead scavenger	81.7	1.6	97.0	2.0
Exports	179.0	3.4	167.3	3.5
Preparation of polysulfides	0.5	--	--	--
Paints, coatings and adhesives	1.36	--	--	--
Extraction solvents	1.05	--	--	--
Cleaning of fabric and polvinyl chloride equipment	0.91	--	--	--
Grain fumigation	0.46	--	--	--
Other uses	0.46	--	6.8	0.1
Total	5199.44	99.8	4804.4	99.9

[a] Seufert et al., 1980; Blackford, 1974

TABLE 5-5

Users of Ethylene Dichloride for Intermediate Purposes[a]

	1,1,1-Trichloroethane	Trichloroethylene	Perchloroethylene	Ethyleneamines	Vinylidene Chloride
Dow Chem. USA					
Freeport, TX	X	X	X	X	X
Plaquemine, LA	X	---	X	---	X
PPG Industries					
Lake Charles, LA	---	X	X	---	X
Union Carbide Co.					
Taft, LA	---	---	---	---	X
Texas City, TX	---	---	---	---	X
Diamond Shamrock Corp.					
Deer Park, TX	---	---	X	---	---
E.I. duPont					
Corpus Christi, TX	---	---	X	---	---

[a] SRI, 1983; Blackford, 1974
X = produces this chemical from ethylene dichloride

Exports of EDC have been increasing in recent years (see Table 5-6). Exports may grow by as much as 8% per year through the mid-80s (CMR, 1983). The Japanese are expected to become major importers as they close down significant amounts of mercury cell chlor-alkali capacity because of environmental regulations. However, part of that demand will be filled by Shell's one billion pounds/year EDC plant in Jubail, Saudi Arabia, which is due on stream in 1985.

EDC has a variety of relatively small miscellaneous uses. It is used as a solvent in applications that include textile and PVC cleaning, metal degreasing, extractions, and use in paints, coatings and adhesives. As an intermediate, EDC is used to produce polysulfide elastomers and ethylenimine (aziridine). Dow chemical captively consumes several million pounds per year of EDC at their Freeport, TX, facility to produce ethylenimine. EDC is used as a grain fumigant; Auerbach Associates (1978) estimated grain fumigant uses in grain; Metcalf (1981) lists EDC as a fumigant for use in household and soil applications. Other uses mentioned for EDC include varnish and finish removers, soaps and scouring compounds, wetting and penetrating agents and ore flotation (Hawley, 1981).

5.5. SOURCES OF EMISSIONS

EDC can enter the environment through atmospheric emissions, waste effluents to waterways, and land disposals of liquid and solid wastes. EDC in liquid and solid waters evaporates rapidly because of its high volatility; consequently, releases to land and water can be expected to predominantly enter the atmosphere. The sources of EDC emissions are during EDC manufacture, intermediate use of EDC in production of other chemicals, and dispersive uses of EDC in end-point product applications.

A number of estimates have been generated which predict the amount of EDC that is released to the environment. These estimates are based, in large part, on a sampling of monitoring data and a variety of engineering estimates. In many instances, the impact of current control technology may not have been adequately assessed. Therefore, the estimates that have been generated for EDC releases should not be interpreted as exact measurements, but are best regarded as order of magnitude estimates. Estimates of releases are in Table 5-6.

Table 5-6 lists sources of EDC emissions in 1979 and estimates of the amounts released in air, water, and solid waste. Total 1979 emissions to the atmosphere, water, and solid waste amounted to 12,238 metric tons. The data in Table 5-6 indicate that gaseous emissions from EDC production amounted to 52.3% of total atmospheric releases, while feedstock uses, dispersive applications, and exports accounted for 12.6, 33.6, and 1.5%, respectively (Seufert et al., 1980).

Utilizing data from EDC producers, state and local emissions control agencies, and the open literature, Hobbs and Key (1978) estimated 1978 emissions of EDC at ≈11,000 metric tons. The degree of current emissions control on domestic processes involved in the primary production of EDC was assessed by Hobbs and Key (1978).

Estimates by SRI International (U.S. EPA, 1979a) indicated that total domestic emissions of EDC from primary production, fugitive sources, and tank storage are 44,000 metric tons or ≈0.8% of the amount produced. The impact of current control technology was not addressed in the report.

Eimutis and Quill (1977) estimated process emissions of EDC for 1977 at 50,000 metric tons. Presumably, this estimate did not take into account current control technology.

For 1974, Patterson et al. (1975) estimated total domestic emissions at 74,000 metric tons. Total domestic emissions for 1973 were reported at 54,000 metric tons by Shamel et al. (1975). The sources of EDC releases are discussed below.

TABLE 5-6

Estimated Environmental Releases of Ethylene Dichloride in 1979[a]

Application	Releases (metric tons)		
	Air	Water	Solid waste
Production of 1,2-dichloroethane	6,154	61	---
Indirect production	65	191	---
Feedstock uses			
Trichloroethylene	73	---	---
Tetrachloroethylene	138	---	---
1,1-Dichloroethylene	86	---	---
Ethyleneamines	104	---	---
Preparation of polysulfides	5	---	5
Vinyl chloride	136	---	---
Exports	180	---	---
Dispersive uses			
Lead scavenging	956	---	---
Fabric and PVC equipment cleaning	864	---	46
Paints, coatings, adhesives	1,364	---	---
Extraction solvents	1,000	---	50
Grain fumigation	460	---	---
Miscellaneous uses	300	---	---
Total	11,885	252	101

[a] Seufert et al., 1980

5.5.1. Production and Related Facilities. In general, EDC is produced commercially at an integrated manufacturing facility which uses some or all of the produced EDC to make vinyl chloride and, in some cases, other derivatives. In a typical vinyl chloride manufacturing facility, waste streams are generated by the three distinct processes: direct chlorination of ethylene, oxy-chlorination of ethylene, and dehydrochlorination to vinyl chloride, these are typically combined at a given facility for recovery, treatment and disposal. The specific number of point sources of releases at a manufacturing site is a function of plant design. Point sources of EDC loss from an integrated vinyl chloride plant include direct and oxy-chlorination reactor vent streams, light-ends distillation column vent, heavy-ends from the EDC recovery tower, wastewater from drying columns and scrubbers, and fugitive emissions from storage, pumps, seals, etc. (Catalytic, 1979; U.S. EPA, 1979b). Releases from these manufacturing sites are mostly to the atmosphere and arise largely from vent gas streams (U.S. EPA, 1979b). Control devices used to limit EDC escape to the atmosphere include thermal oxidizers, catalytic oxidizers, vent condensers, scrubbers, and vent gas post-reactors (Hobbs and Key, 1978).

Combined wastewaters which are generated from EDC manufacture (vent gas scrubbers, water produced during oxy-chlorination, and washwater) are treated in several ways depending upon the plant (Catalytic, 1979). Treatments include pretreatment and steam stripping prior to biological treatment, incineration of a portion of the waste stream, neutralization and chemical treatment, secondary treatments and final discharges to surface waters, to public owned treatment works, or to deep-well injection. Estimates of the amounts of EDC released to the surface waters are dependent upon engineering estimates of the overall success of treatments and the volume of wastewater flow.

Solid wastes generated at an integrated vinyl chloride plant are usually treated to recover organic compounds present. Wastes are subsequently disposed of in a landfill or incinerated, recovering chlorine as hydrogen chloride (McPherson et al., 1979). Some solid wastes, possibly tars and heavy-ends, may be a suitable feedstock for tetrachloroethylene/carbon tetrachloride via a chlorination process.

5.5.2. Dispersive Uses.

5.5.2.1. LEAD SCAVENGING -- Seufert et al. (1980) estimated that 956 metric tons of EDC were released to the environment in 1979 from lead scavenging applications. Releases occur during blending of the gasolines, refueling of automoblies, filling and evaporation from gasoline storage tanks, and combustion of the gasoline. Approximately 1% of the EDC used for lead scavenging is estimated to be released into the environment; the remainder is converted to hydrogen chloride and then to lead chloride during combustion.

5.5.2.2. PAINTS, COATINGS, ADHESIVES -- In this application, EDC is used as a solvent that is allowed to evaporate. Therefore, all of the EDC is emitted to the environment.

5.5.2.3. GRAIN FUMIGATION -- Fumigants are defined as gaseous pesticides. They must remain in the gas or vapor state and in sufficient concentration to be lethal to the target pest species. Therefore, all of the EDC used for this purpose will be vented to the atmosphere, as there are no control methods used.

5.5.2.4. FABRIC AND PVC CLEANING -- It is presumed that most EDC used for cleaning purposes will eventually be emitted to the atmosphere. Some cleaning wastes from PVC reactors may be drummed for landfill disposal.

5.5.2.5. OTHER DISPERSIVE USES -- In other dispersive uses, it has been assumed that most EDC will eventually be emitted to the atmosphere. Some may be landfill, as with extraction solvents, and some may be incinerated.

5.5.3. Conclusions. The major sources of EDC emissions are from vent gas streams released during the manufacture of EDC and subsequent integrated production of vinyl chloride monomer, and other EDC derivatives. Significant amounts of EDC are also released to the environment from dispersive uses. In 1979, an estimated 6,696 metric tons of EDC were released to the atmosphere from EDC production and feedstock uses, while an estimated 4,944 metric tons were released to the atmosphere from dispersive uses (see Table 5-6).

6. FATE AND TRANSPORT IN THE ENVIRONMENT

The fate and transport of EDC in the environment depend on the medium in which it is present. The fate and transport of EDC in three environmental media (atmosphere, water and soil) are discussed below. Since a large percent of EDC emitted into the environment is in the atmospheric medium (see Chapter 4), the fate and transport of the chemical in this medium deserve special attention.

6.1. ATMOSPHERE

The fate of EDC in the atmosphere is dictated by its ability to undergo chemical and physical removal processes in this medium. Reaction with •OH radicals is the principal chemical process by which many organic compounds including EDC are removed from the atmosphere (Crutzen and Fishman, 1977; Singh, 1977; Altshuller, 1979; Cupitt, 1980). Photolysis of O_3 in the troposphere produces singlet atomic oxygen $[O^1{}_D]$ that then reacts with water vapor to produce •OH radicals. The tropospheric half-life ($t_{1/2}$) of a compound is related to the •OH radical concentration according to the expression:

$$t_{1/2} = \frac{0.693}{K[\cdot OH]}$$

where K is the rate constant of the reaction and [•OH] is the concentration of •OH radicals.

It is obvious from the above equation that an estimation of the tropospheric half-life for EDC due to •OH radical reaction requires that the values of both K and [•OH] be known. There are only two measurements of EDC reaction rate constant with •OH radicals. The absolute rate constant for EDC reaction with •OH radicals was determined by Howard and Evenson (1976) in a conventional discharge flow system. The value of the rate constant obtained in the system at pressures

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ranging from 0.7 to 7 mm Hg and at a temperature of 23°C was 22 ± 5 (standard deviation of average) cm^3 $molecule^{-1}$ sec^{-1}.

The rate constant for the reaction of •OH radicals with EDC in the presence of O_2 and N_2 was determined by Butler et al. (1978). At 29.5°C and a total pressure of 400 mm Hg, the reaction rate constant was determined to have a probable value of 6.5×10^{-14} cm^3 $molecule^{-1}$ sec^{-1} with an upper limit value of 29×10^{-14} cm^3 $molecule^{-1}$ sec^{-1}. Although Butler et al. (1978) argued that the presence of oxygen and nitrogen at a pressure of 400 mm Hg was more representative of actual tropospheric conditions, the presence of O_2 and N_2 actually complicated the reaction scheme through side reactions and made the extraction of kinetic data more difficult. It is for this reason that Butler et al. (1978) failed to determine the precision of the determined rate constant value. Therefore, the measured rate constant value of 22.0 ± 5 cm^3 $molecule^{-1}$ sec^{-1} for EDC reaction with •OH radicals as reported by Howard and Evenson (1976) appears to be more accurate than the value of 6.5×10^{-14} cm^3 $molecule^{-1}$ sec^{-1} as given by Butler et al. (1978).

In Table 6-1, the rate constants for a number of chlorinated ethanes, including EDC, at room temperature have been shown. It seems clear from this table that a value of 22.0×10^{-14} cm^3 $molecule^{-1}$ sec^{-1} is more consistent with the measured K values for other chlorinated ethanes than a value of 6.5×10^{-14} cm^3 $molecule^{-1}$ sec^{-1}.

On the basis of the above discussion, it is reasonable to accept a value of 22×10^{-14} cm^3 $molecule^{-1}$ sec^{-1} as the rate constant value for EDC reaction with •OH radicals at 296°K (room temperature).

It should be recognized that the value of K is dependent on temperature. The temperature in the troposphere is dependent on latitude, altitude and seasonal variations. The average annual tropospheric temperature weighted over

TABLE 6-1

Rate Constants for a Few Chlorinated Ethanes at Room Temperature

Compound	Rate Constant 10^{14} cm^3 $molecule^{-1}$ sec^{-1}	Reference
CH_3CH_2Cl	39, 44	Howard and Evenson, 1976; Butler et al., 1978
CH_3CHCl_2	26	Howard and Evenson, 1976
CH_2ClCH_2Cl	22, 6.5	Howard and Evenson, 1976; Butler et al., 1978
$CH_2ClCHCl_2$	33	Singh et al., 1981

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those variables is close to 265°K, or -8°C (Altshuller, 1979). Therefore, the evaluation of reaction rate at this temperature representing an average tropospheric reaction rate must incorporate the rate constant value at 265°K. When the rate constant is not known, Altshuller (1979) estimated it by dividing the K value at 298°K by 1.75. This is an empirical relationship and is applicable only to saturated organic compounds. Therefore, the rate constant for EDC reaction with •OH at 265°K can be estimated as $\frac{22 \times 10^{-14}}{1.75}$ cm^3 $molecule^{-1}$ sec^{-1} or 12.6 cm^3 $molecule^{-1}$ sec^{-1}.

The second factor required for the evaluation of tropospheric half-life for EDC reaction with •OH radicals is the average •OH concentration. Besides hemispheric difference, the concentration of •OH radicals in the troposphere is dependent on latitude, altitude and seasonal variations. The concentration of tropospheric •OH radicals in the Northern Hemisphere across the latitudes of the continental United States has been estimated by different investigators to range from 0.2 to 0.9 x 10^6 molecules cm^{-3} annually (Logan et al., 1981; Crutzen and Fishman, 1977; Neely and Plonka, 1978). Singh et al. (1983) have recently estimated a mean hydroxyl radical concentration of 0.4-0.6 x 10^6 molecules cm^{-3} over the troposphere of continental United States. Therefore, a value of 0.5 x 10^6 molecules cm^{-3} is a good estimate for the average tropospheric hydroxyl radical concentration over the continental United States. It should be emphasized that the •OH concentration can vary substantially from the average value of 0.5 x 10^6 molecules cm^{-3}. Calvert (1976) estimated the average ambient level of •OH radicals in the morning hours in Los Angeles to be ≈ 2.6 ± 2 x 10^6 molecules cm^{-3}. Assuming equal periods of daylight and darkness, the average concentration for a 24-hour day should be ≈1 x 10^6 molecules cm^{-3}.

The calculations of tropospheric half-life for EDC reaction with •OH radical can be made under two scenarios. In the first case, a rate constant value at ambient temperature (22 x 10^{-14} cm^3 $molecule^{-1}$ sec^{-1}) and an

•OH concentration of 1×10^6 molecule cm^{-3} can be used to derive the half-life value of 36 days. In the second case, a rate constant value of 265°K corresponding to annual average tropospheric temperature over continental United States (12.6×10^{-14} cm^3 $molecule^{-1}$ sec^{-1}) and a value of •OH concentration of 0.5×10^6 molecules cm^{-3} corresponding to the annual average tropospheric concentration of •OH radical over continental United States can be used to derive a half-life value of 127 days. Therefore, the tropospheric half-life for EDC reaction with •OH may vary from 36 to 127 days.

The reactivity of EDC with chlorine atoms was studied by Spence and Harst (1978). These investigators found that the chlorine-sensitized photooxidation of 10 ppm EDC with 4 ppm Cl_2 at 22.5°C and irradiated by UV lamp (365 nm wavelength max.) and sun lamp (310 nm wavelength max.) produced a number of reaction products. Although hydrochloric acid (6.5 ppm), carbon monoxide (1 ppm), formyl chloride (3.5 ppm), CO_2 (2 ppm) and chloroacetyl chloride (0.5 ppm) were formed, no phosgene could be detected as a reaction product. EDC was found to have a relatively low reactivity towards Cl atoms compared to other chlorinated ethanes.

That a chlorine-sensitized photooxidation is representative of actual tropospheric conditions has been contested by Singh (1978). This investigator estimated that chlorine atom concentrations in simulation chambers can be 10^3 to 10^6 times larger than in the troposphere. Thus, the role of chlorine atoms would be minimal under actual tropospheric conditions where •OH radicals are predominant.

The role of halocarbons in the catalytic destruction of ozone (O_3) is well documented (Altshuller, 1979; Altshuller and Hanst, 1975). Any halogenated compound with a sufficiently long lifetime may be transported to the stratosphere where photolytic mechanisms may release halogen atoms to participate in the destruction of O_3. The rate of reaction of •OH with halocarbons is one mechanism which competes with stratospheric photolysis as a halocarbon sink.

Since transport to the stratosphere is a relatively slow process, the reported half-life for EDC suggests that only a small fraction released in the troposphere will reach the stratosphere. Thus, emissions of EDC would not be expected to play a significant role in the catalytic destruction of ozone. However, in the view of Altshuller and Hanst (1975), EDC should be considered a threat in this regard since the production volume of EDC is so large. These investigators cite chloroacetyl chloride as the sole product of EDC reaction with •OH. The possibility that this reaction product may have sufficient stability to travel to the stratosphere was raised. If formed in the troposphere, most of the chloroacetyl chloride probably will be washed out by rain. If it travels to the stratosphere, however, it may undergo photodissociation to form atomic chlorine.

The three most likely physical processes that may participate in the removal of EDC from the atmosphere were studied by Cupitt (1980). The half-life for EDC removal by rain droplets was estimated to be 390 years. EDC in the vapor phase may be adsorbed on aerosol particles and removed from the atmosphere with the aerosol. However, the half-life of this removal process was estimated to be ≈13 years (Cupitt, 1980). It has been estimated by Cupitt (1980) that compounds with saturation vapor pressures of $<10^{-7}$ mm Hg are likely to be adsorbed on atmospheric aerosols. Since the vapor pressure of EDC is much higher, it is not expected to be adsorbed by aerosol and the probability of its removal by this process seems to be remote.

The third physical removal mechanism, dry deposition of EDC, was also studied by Cupitt (1980). He estimated a half-life value of 25 years for this process. Therefore, it is not expected to be a significant EDC removal mechanism from the atmosphere.

It is apparent from the above discussion that physical processes are not significant for the removal of EDC from the atmosphere. Of the chemical processes, the most significant reaction that may account for the partial removal of EDC from the atmosphere is its reaction with •OH radicals. The half-life for the process has been estimated to be ≈36 to 127 days. Therefore, it is anticipated that EDC will persist for a relatively long time in the atmosphere and may participate in intramedia transport from its source of emissions.

6.2. AQUATIC MEDIA

The fate of EDC in aquatic media is expected to be determined by its chemical, physical and microbiological removal mechanisms. The fate of EDC with respect to its possible chemical reactions has been reported by Callahan et al. (1979). Both photolysis and hydrolysis of EDC in aquatic media are expected to be insignificant fate processes (Callahan et al., 1979). Based on the oxidation rate constant data given by Mabey et al. (1981) and the concentration of free radicals in aquatic media given by Mill et al. (1982), the oxidation of EDC by singlet oxygen ($K<<360\ M^{-1}\ hr^{-1}$) and peroxy radicals ($1\ M^{-1}\ hr^{-1}$) can be predicted to be environmentally insignificant processes.

The degradation possibilities of EDC by microorganisms in aquatic media have been studied by several authors. From the results of the laboratory tests conducted by several investigators with activated sludge or sewage seed as microbial inoculum in aquatic media, it can be concluded that EDC may biodegrade slowly under these conditions (Price et al., 1974; Tabak et al., 1981; Ludzack and Etlinger, 1960; Henckelikian and Rand, 1955; Stover and Kincannon, 1983). Under anoxic conditions, Bouwer and McCarty (1983) observed very little degradation of EDC with anaerobic inoculum. In a river die-away test, Mudder et al. (1982) reported no degradation of EDC at concentrations of ≈1 ppm and above. It can be concluded from these discussions that biodegradation will be an insignificant fate process for EDC in ambient aquatic media.

The two likely physical processes that may remove EDC from aquatic media are sorption and volatilization. The removal of EDC by sorption on sediments and the subsequent sedimentation is probably not a significant process (Callahan et al., 1979; Mabey et al., 1981). A calculation based on EXAMS modeling by the method of Burns et al. (1982) with the input parameters given in Section 3 also shows that EDC is not likely to be significantly sorbed onto particulate matter in water.

The evaporation half-life for EDC from water at a depth of 1.6 cm, a concentration of 2 ppm, and a temperature of 24°C was estimated to be 8 minutes under stirring (Chiou et al., 1980). Under more realistic conditions of a wind speed of 3 m/sec, water current of 1 m/sec, and a water depth of 1 m, Lyman et al. (1982) calculated the evaporation half-life of EDC as 4 hours.

The bioconcentration factor (BCF) for EDC in aquatic organisms was estimated as 6.03 by Kenaga (1980) from the water solubility and a linear regression equation. In a 14-day exposure experiment with bluegill sunfish (Lepomis macrochirus), Barrows et al. (1980) determined a BCF of 2.0 for this compound. Therefore, EDC is not likely to bioconcentrate in aquatic organisms.

It can be concluded from the discussion above that the primary removal mechanism of EDC from aquatic media is probably volatilization. The half-life for volatilization is such that the compound may persist in aquatic media for a reasonable period and may participate in transport in aquatic bodies.

6.3. SOIL

Data pertaining to the fate of EDC in soil are very limited. If one considers the chemical reactivity of EDC in aquatic media (see Section 6.2), it is possible to speculate that chemical reactions of EDC may be faster in soil than in water, particularly with soil acclimatized with EDC. However, Wilson et

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al. (1981) found virtually no biodegradation of EDC with soils collected near Ada, OK, that contained an average sand of 92% and organic carbon of 0.09%.

The sorption constant (K_{oc}) of EDC on soils was predicted by Kenaga (1980) to be 43 (standardized with respect to soil organic content) from regression equation and solubility of this chemical in water. Chiou et al. (1979) estimated a value of 19 for K_{oc} with Williamette silt loam containing 1.6% organic matter, 26% clay, 3.3% sand and 69% silt. Therefore, the compound is not expected to be sorbed strongly onto soils, particularly onto soils containing low organic matter, and may percolate through the soil column. This has been confirmed by Wilson et al. (1980), who found ≈50% percolation of EDC through a column of 140 cm depth containing the previously described Oklahoma soil. The fact that Page (1981) reported the detection of EDC in 10% groundwater samples in NJ also indicates that the compound may transport downwards through some soils.

The volatilization of EDC from soil may be an important removal mechanism. However, very few investigative data are available on this subject. Again, if one considers the investigation of Wilson et al. (1981) that reported the loss of 50% EDC from the soil column through volatilization, one can conclude that volatilization may be one of the most significant physical removal processes for EDC from soil

6.4. SUMMARY

Based on available kinetic data and average tropospheric hydroxyl free radical concentration, the half-life of EDC, the most likely removal mechanism for EDC from the atmosphere, has been estimated to range from 36 to 127 days. Due to different factors that may cause variations in •OH concentrations in the troposphere, the persistence of EDC could vary somewhat from the estimated value. Chloroacetyl chloride is probably the principal product resulting from the reaction of EDC with •OH radicals.

EDC is not expected to play a significant role in stratospheric ozone destruction reactions due to its relatively short tropospheric half-life. However, chloroacetyl chloride may have suffficient stability to diffuse to the stratosphere and may participate in UV reactions producing chlorine atoms.

In the aquatic environment, the most significant removal mechanism appears to be its volatilization. The half-life for this process has been estimated to be ≈ 4 hours. Therefore, EDC may persist in the aquatic media for a reasonable period and may participate in its transport in water bodies.

From the little information that is available regarding the fate of EDC in soil, it has been concluded that both volatilization from and leaching through soil are the two significant removal mechanisms for EDC.

7. ENVIRONMENTAL LEVELS AND EXPOSURE

7.1. ENVIRONMENTAL LEVELS

EDC contamination of the environment can result from the manufacture, use and disposal of the chemical. Sources of environmental release and quantitative estimates of releases are discussed in Section 5 of this report. This section is concerned with the levels of EDC that have been detected in various areas and monitoring sites. Sizeable quantities of EDC are judged to be released to the air during manufacture and conversion to vinyl chloride at an integrated manufacturing site. This judgement is borne out by the high ambient concentrations of EDC found near several of these sites.

7.1.1. Atmospheric Levels. In addition to atmospheric releases of EDC from manufacture and feedstock uses, EDC can be released to the air from dispersive uses such as grain fumigation, solvent uses in paints, coating and adhesives, cleaning applications, and gasoline uses related to lead scavenging.

Recent air monitoring data for EDC are listed in Table 7-1. These data indicate that EDC is often present in ambient air in urban and industrial areas, especially near plants manufacturing or using the chemical. Recent measurements made at sites in three geographical areas central to EDC production and user facilities indicated EDC concentrations as high as 184 ppb (Elfers, 1979). These levels were associated with industrial sources and occurred during atmospheric conditions of calm or low wind speeds. Measurements were made during 10 to 13 day periods at Lake Charles and New Orleans, LA, and at Calvert City, KY. The highest concentrations were reported for the Lake Charles area, with the highest single concentration being 184 ppb and the average detectable concentration being 27.5 ppb. In Calvert City, ambient concentrations ranged from <0.12 to

TABLE 7-1

Ambient Atmospheric Levels of Ethylene Dichloride

Location	Type of Site	Date	Analytical Method	Number of Samples	Concentration (ppt, v/v)[a] Max.	Min.	Avg.	Reference
ALABAMA								
Birmingham		April, 1977		2	98.6	50.7	74.7	Pellizzari and Bunch, 1979
Birmingham		April, 1977		7 (4 ND)	99	0	35	Pellizzari, 1979a
ARIZONA								
Phoenix	urban		GC/ECD		1451.1	38.8	216.3	Singh et al., 1980
Grand Canyon	rural	Nov-Dec 1977		7 (7 ND)	---	---	---	Pellizzari, 1979a
CALIFORNIA								
Domingues		May, 1976		1	---	---	3662.3	Pellizzari and Bunch, 1979
Los Angeles	urban		GC/ECD		1354.8	173.0	519.2	Singh et al., 1980
Oakland	urban	Aug-Sept 1977	GC/ECD		843.0	38.3	82.5	Singh et al., 1980
Riverside		August, 1980	GC/ECD	102	580	89	360	Singh et al., 1980
Upland				8	212.9	61.8	110.3	Pellizzari and Bunch, 1979
Upland		Aug-Sept 1977		16 (14 ND)	210	0	27	Pellizzari, 1979a
COLORADO								
Denver		June, 1980	GC/ECD	95	480	100	240	Singh et al., 1980
ILLINOIS								
Chicago		April, 1981	GC/ECD	NR	2820	22	195	Singh et al., 1982
KENTUCKY								
Calvert City	12 sites near chem. plant	Aug-Sept 1978		156	17849.2	0	1631.6	Suta, 1979
Calvert City		Aug-Sept 1978	GC/MS	88	17800	<120	5000	Elfers, 1979
LOUISIANA								
Baton Rouge		March, 1977		25 (9 ND)	630	0	270	Pellizzari et al., 1979
Baton Rouge		March, 1977	GC/MS	18 (2 ND)	2556.5	19.3	429.4	Pellizzari, 1978a
Geismar	Industrial	Feb, Mar 1977		10 (1 ND)	2554.5	24.7	760.4	Pellizzari, 1978a
Iberville Parish		Jan, Feb 1977		11	1164.2	2.2	320.9	Pellizzari, 1978a
Lake Charles		June-Oct 1978		98	61000	150	27000	Pellizzari, 1979b

TABLE 7-1 (cont.)

Location	Type of Site	Date	Analytical Method	Number of Samples	Concentration (ppt, v/v)[a] Max.	Min.	Avg.	Reference
LOUISIANA (cont.)								
Lake Charles		June, 1978		6	307.3	5.2	86.5	Pellizzari and Bunch, 1979
Lake Charles		Sept-Oct 1978	GC/MS	110	184000	<120	27500	Elfers, 1979
Lake Charles	12 sites near chem. plant	Sept, Oct 1978		144	191545.6	0	18121.2	Suta, 1979
New Orleans		October, 1978	GC/MS	91	41700	<120	2900	Elfers, 1979
New Orleans	near chem. plant	October, 1978		120	40222.6	0	1780.0	Suta, 1979
Plaquemine		Jan, Feb 1977		11	921.4	2.2	337.2	Pellizzari and Bunch, 1979
MISSOURI								
St. Louis		May-June 1980	GC/ECD	90	260	65	120	Singh et al., 1980
NEW JERSEY								
Batsto	rural	Feb-Dec 1979	GC/FID-ECD-MS	42 (40 ND)	---	---	Trace (2 samples)	Bozzelli et al., 1980
Bound Brook	off highway	March, 1976		1	---	---	Trace	Pellizzari and Bunch, 1979
Bridgeport		September, 1977		2	---	---	Trace	Pellizzari and Bunch, 1979
Bridgewater		July-Aug 1978		22 (18 ND)	380	0	170	Bozzelli et al., 1979
Burlington		September, 1977		1	---	---	Trace	Pellizzari and Bunch, 1979
Camden	urban	Apr-Oct 1979	GC/FID-EDC-MS	23 (21 ND)	---	---	Trace (2 samples)	Bozzelli et al., 1980
Carlstadt		September, 1979	GC/MS	16 (7 ND)	998.0	33.4	537.2	Pellizzari, 1978b
Clifton		March, 1976		1	---	---	15950	Pellizzari and Bunch, 1979
Deepwater	near chem. plant	June, 1977		6 (3 traces)	13.1	5.9	7.4	Pellizzari and Bunch, 1979
East Brunswick	marina	July, 1976		2	85.8	37.1	61.6	Pellizzari and Bunch, 1979
Edison		Mar-July 1976		33 (20 ND)	3400	8.6	1600	Pellizzari and Bunch, 1979
Edison	near waste disposal area	Mar-July 1976		16 (1 trace)	14091.5	53.6	2712	Pellizzari and Bunch, 1979

TABLE 7-1 (cont.)

Location	Type of Site	Date	Analytical Method	Number of Samples	Concentration (ppt, v/v)[a] Max.	Min.	Avg.	Reference
NEW JERSEY (cont.)								
Elizabeth		Sept 1978-Dec 1979	GC/FID-ECD-MS	71 (53 ND)	2200	0	220	Bozzelli et al., 1980; Pellizzari, 1979a
Elizabeth	near industrial plant	Jan-Dec 1979	GC/FID-ECD-MS	54 (7 trace, 46 ND)	---	---	2202.7	Bozzelli et al., 1980
Fords		March, 1976		1	---	---	Trace	Pellizzari and Bunch, 1979
Hoboken		March, 1976		2 (2 ND)	0	0	0	Pellizzari, 1977a; Pellizzari et al., 1979
Linden	industrial	June, Nov 1977		16 (1 trace)	48.2	2.0	14.3	Pellizzari and Bunch, 1979
Linden		June, 1977	GC/MS	11 (1 ND)	4.9	4.9	4.9	Pellizzari, 1978c
Middlesex		July, 1978		18 (13 ND)	290	28	110	Bozzelli et al., 1979
Newark	urban	Jan-Dec 1979	GC/FID-ECD-MS	37 (9 trace, 28 ND)	---	---	Trace	Bozzelli et al., 1980
Newark	urban	March, 1976		1	---	---	Trace	Pellizzari and Bunch, 1979
Newark	urban	Mar 1976-Dec 1979		160 (112 ND)	5800	0	450	Bozzelli and Kebbekus, 1979; Bozzelli et al., 1980; Pellizzari, 1977
Passaic		March, 1976		1	---	---	Trace	Pellizzari and Bunch, 1979
Paterson		March, 1976		1	---	---	Trace	Pellizzari and Bunch, 1979
Rahway		September, 1978		16	775.5	165.4	525.8	Pellizzari, 1978b,d
Rutherford		May 1978-Dec 1979	GC/FID-ECD-MS	196 (141 ND)	3200	0	370	Bozzelli et al., 1979, 1980
Rutherford	suburban	May, 1979		46 (3 trace, 42 ND)	---	---	593.3	Bozzelli et al., 1980
Sayreville		July, 1976		1	---	---	9372.8	Pellizzari and Bunch, 1979
Somerset		July, 1978		29 (17 ND)	1800	0	490	Bozzelli et al., 1979
South Amboy	industrial	Jan-Dec 1979		48 (4 trace, 44 ND)	---	---	Trace	Bozzelli et al., 1980
NEW YORK								
Niagara Falls	residential (Love Canal)	February, 1978		9 (2 trace, 7 ND)	---	---	Trace	Pellizzari, 1978c,d
Staten Island	urban	November, 1976		3	50.7	46.0	48.2	Pellizzari and Bunch, 1979
Staten Island		Mar-Apr 1981	GC/ECD	NR	4312	55	256	Singh et al., 1982

TABLE 7-1 (cont.)

Location	Type of Site	Date	Analytical Method	Number of Samples	Concentration (ppt, v/v)[a] Max.	Min.	Avg.	Reference
NORTH CAROLINA								
Chapel Hill		June, 1980		6	110	110	110	Wallace, 1981
OKLAHOMA								
Liberty Mound		July-Sept 1977		2 (2 ND)	0	0	0	Pellizzari, 1978e
Tulsa		July-Sept 1977		2 (2 ND)	0	0	0	Pellizzari, 1978e
Vera		July, 1977		1 (1 ND)	0	0	0	Pellizzari, 1978e
PENNSYLVANIA								
Bristol		August, 1977		2	---	---	63.8	Pellizzari and Bunch, 1979
Marcus Hook		August, 1977		2	---	---	48.2	Pellizzari and Bunch, 1979
N. Philadelphia		August, 1977		4	238.6	41.3	139.2	Pellizzari and Bunch, 1979
Pittsburgh	urban	April, 1981	GC/ECD	NR	237	66	121	Singh et al., 1982
TEXAS								
Aldine		June-Oct 1977		3 (3 ND)	0	0	0	Pellizzari et al., 1979
Beaumont		March, 1980		11	670	670	670	Wallace, 1981
Deer Park	industrial	August, 1977		6 (3 trace)	16390.6	1002.5	6353.5	Pellizzari and Bunch, 1979
El Paso		Apr-May 1978		22 (19 ND)	29	0	4.3	Pellizzari, 1979a
Freeport	industrial	August, 1977		2	1112.5	815.8	964.2	Pellizzari and Bunch, 1979
Houston		July 1976-May 1980	GC/ECD	99 (5 ND)	3000	50	1300	Pellizzari et al., 1979 Singh et al., 1980
Houston	urban	NR		30	16390.6	73.4	893.0	Pellizzari, 1978b
Houston	streets, parks, rural highway	July 1976, June, July 1978		10 (1 trace)	109.8	30.4	63.0	Pellizzari and Bunch, 1979
La Porte		August, 1976		1	---	---	192.3	Pellizzari and Bunch, 1979
Pasadena		July, 1976		1	39	39	39	Pellizzari et al., 1979
UTAH								
Magna		Oct-Nov 1977		9 (9 ND)	0	0	0	Pellizzari, 1979a

TABLE 7-1 (cont.)

Location	Type of Site	Date	Analytical Method	Number of Samples	Concentration (ppt, v/v)[a] Max.	Min.	Avg.	Reference
VIRGINIA								
Front Royal		Oct, Nov 1977		16	86.0	37.3	48.2	Pellizzari and Bunch, 1979
WEST VIRGINIA								
Charleston		Sept, Nov 1977		3	---	---	57.1	Pellizzari and Bunch, 1979
Charleston		Sept-Nov 1977	GC/MS	4 (4 ND)	0	0	0	Pellizzari, 1978e
Institute		November, 1977	GC/MS	2 (2 ND)	0	0	0	Pellizzari, 1978e
Institute		November, 1977		3	---	---	37.3	Pellizzari and Bunch, 1979
Nitro		Oct, Nov 1977		4	63.8	37.3	46.7	Pellizzari and Bunch, 1979
Nitro		Sept-Oct 1977	GC/MS	6 (6 ND)	0	0	0	Pellizzari, 1978e
St. Albans		October, 1977		1	---	---	48.2	Pellizzari and Bunch, 1979
St. Albans		Sept-Nov 1977	GC/MS	4 (4 ND)	0	0	0	Pellizzari, 1978e
S. Charleston		Mar, Sept-Nov 1977		6	63.8	37.3	52.4	Pellizzari and Bunch, 1979
S. Charleston		Mar-Nov 1977	GC/MS	16 (15 ND)	37	0	2.3	Pellizzari, 1979a; Pellizzari, 1978e
W. Belle		Sept-Nov 1977	GC/MS	6 (6 ND)	0	0	0	Pellizzari, 1978e
W. Belle		Sept-Nov 1977		4	61.8	37.3	47.0	Pellizzari and Bunch, 1979
WASHINGTON								
Pullman	rural	Dec 1974-Feb 1975	GC/MS	NR	---	<5	---	Grimsrud and Rasmussen, 1975
Pullman	rural	November, 1975	GC/ECD	1	---	10	---	Harsch et al., 1979

[a] Assume ambient temperature of 25°C and atmospheric pressure of 760 mmHg.

ND = Not detected
NR = Not reported
ECD = Electron capture detection
FID = Flame ionization detection
GC = Gas chromatography
MS = Mass spectrometry

17.8 ppb. Levels recorded in the New Orleans study area ranged from <0.12 to 41.7 ppb.

Analyses done by Elfers (1979) were performed by collecting ambient air on charcoal tubes followed by desorption by carbon disulfide. Detection and quantitation was made by gas-chromatograph-mass spectrometry. Quality control check sample analysis indicated that recovery of standard concentrations was highly variable. The detection limit of the gas chromatographic method was reported as 1 µg. The relative standard deviation of replicate standard solutions was found to be 3%. The precision of the analytical and sampling methods together was 6%. The accuracy of the analytical method varied between 72 and 97%.

The highest reported reading for a single sample listed in Table 7-1 is 191.5 ppb, which was recorded in Lake Charles, LA, the site for several EDC-vinyl chloride manufacturing facilities. Concentrations in excess of 15 ppb for a single sample were also reported near manufacturing facilities in Calvert City, KY; New Orleans, LA; Deer Park and Houston, TX.

Recent studies have measured general urban ambient concentrations of EDC in ten cities (Singh et al., 1980, 1981, 1982). The results of these studies are summarized in Table 7-2. The averaging time for the mean concentrations in these studies was 2 weeks. Electron capture detector-gas chromatography was the primary means of analysis.

Low levels of EDC were recorded in a year-long monitoring program of five cities in industrial northern New Jersey (Bozzelli et al., 1980). Samples were collected at the five sites regularly throughout 1979. Only two of the 208 samples analyzed had EDC concentrations higher than trace (41 ng/m^3 or 10 ppt).

In a survey of air contaminants in the rural northwest, Grimsrud and Rasmussen (1975) found EDC concentration of <5 ppt.

TABLE 7-2

Ambient Concentrations of Ethylene Dichloride in Urban Areas[a]

City	Ethylene Dichloride Concentrations (ppt) Mean	Maximum	Minimum
Los Angeles, CA	519	1353	173
Phoenix, AZ	216	1450	39
Oakland, CA	83	842	38
Houston, TX	1512	7300	50
St. Louis, MO	124	607	45
Denver, CO	241	2089	56
Riverside, CA	357	2505	63
Staten Island, NY	256	4312	55
Pittsburgh, PA	121	237	66
Chicago, IL	195	2820	22

[a] Singh et al., 1980, 1981, 1982

7.1.2. Ground and Surface Water Levels. EDC can be released to the water environment via wastewaters generated during production of ethylene dichloride and its derivatives. It is also possible that EDC may be inadvertently produced in the water environment due to chlorination processes of public water supplies or chlorination of sewage or wastewaters (Versar, 1975; Seufert et al., 1980). One chemical reaction which could lead to EDC production during water treatment is the reaction of alkenes with hypochlorite. However, it is expected that industrial discharges to surface water and leaching from solid waste are the primary causes of EDC contamination in drinking water (Letkiewicz et al., 1982). Most discharges of EDC are judged to ultimately reach the atmosphere because of its high volatility (Letkiewicz et al., 1982). The identification and levels of EDC which have been found in the ground and surface water of the U.S. are discussed below.

EDC was reported to be a principal contaminant in finished water in 1975 by Dowty et al. (1975). Because the gas chromatographic peak could not be resolved, it was not possible to quantitate EDC. It was indicated that EDC levels could be increased as a result of the water treatment processes and could pass the treatment plant without removal. The water analyzed in this study was obtained from the Mississippi River.

Deinzer et al. (1978), citing the results of a 1975 national drinking water survey, reported EDC concentrations ranging from 0 to 6 ppb.

While sampling for pollutants in 14 heavily-industrialized river basins in the United States, Ewing et al. (1977) found that EDC was present in 53 of the 204 samples purged for volatile organic analysis. The majority of the 81 purgeable organic compounds detected were C_1 to C_6 halogenated hydrocarbons. Only chloroform, trichloroethylene and tetrachloroethylene were found with greater

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frequencies. Identification was made by a GC-MS procedure. The limit of sensitivity was <1 ppb.

In a compilation of pollutants found in water, Shackleford and Keith (1976) identified EDC as having been found in industrial effluents, in finished drinking water, and in river waters.

Letkiewicz et al. (1982), in a recent study for the U.S. EPA, discuss the results of six federal surveys in which a number of public water supplies were selected for analysis of chemical contaminants, including EDC. The six Federal drinking water surveys providing data on EDC include the National Organics Reconnaissance Survey (NORS), the National Organics Monitoring Survey (NOMS), the National Screening Program for Organics in Drinking Water (NSP), the 1978 Community Water Supply Survey (CWSS), the Groundwater Supply Survey (GWSS), and the Rural Water Survey (RWS). All surveys sampled both ground and surface waters except for the GWSS. The scope and methodology of each survey is outlined below, along with the identification of EDC presence.

The National Organics Reconnaissance Survey (NORS) was conducted in 1975 to determine the extent of the presence of EDC, carbon tetrachloride, and four trihalomethanes in drinking water supplies from 80 cities across the country (Symons et al., 1975). Another stated objective of the study was to determine the effect of raw water source and treatment practices on the formation of these compounds. The water samples were collected in 50 ml sealed vials, with volatilization prevented by the absence of head space. Samples were subsequently shipped on ice to the EPA Water Supply Research Lab in Cincinnati for analysis. Analyses were performed by purge-and-trap gas chromatography with an electrolytic conductivity detector. A population base of 36 million from 80 cities across the country was covered during the study.

In the NORS study, 16 groundwater systems were analyzed for EDC contamination. None of the 16 systems contain detectable levels. Of the 64 surface water samples analyzed for EDC, six were found to contain quantifiable levels of EDC at 0.2-6.0 mg/ℓ.

The National Organics Monitoring Survey (NOMS) was instituted to identify contaminant sources, to determine the frequency of occurrence of specific drinking water contaminants, and to provide data for the establishment of maximum contaminant levels (MCL's) for various organic compounds in drinking water (U.S. EPA, 1977). The NOMS was conducted in three phases, March-April 1976, May-July 1976, and November 1976-January 1977. Drinking water samples from 113 communities were analyzed for 21 different compounds by purge-and-trap gas chromatography with electrolytic conductivity detectors. During Phase I the samples were collected in 25- or 40-mℓ open-top screw cap septum vials with no head space, a feature that prevented volatilization of the compounds of interest. These samples were then stored at 2-8°C for 1-2 weeks prior to analysis. Samples were collected in a similar fashion for Phases II and III, but were held at 20°C for periods up to 6 weeks. Sodium thiosulfate was added to a number of samples from Phases II and III to reduce any residual chlorine present.

Of 18 groundwater systems analyzed for EDC during Phase I of the NOMS study (March to April 1976), none contained quantifiable levels. When these systems were sampled again during Phase II (May to July 1976), one system was found to contain EDC, at 0.02 µg/ℓ. No detectable levels of EDC were found during Phase III of the study (November 1976 to January 1977).

In Phase I of the NOMS (March to April 1976), water samples from 87 surface water systems were analyzed for EDC. Of these 87 systems, only one was found to contain EDC, at 2.0 µg/ℓ. When these systems were sampled again during the second phase of the survey, one was found to be contaminated, at 1.8 µg/ℓ.

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During the third phase of the NOMS (November 1976 to January 1977), analyses revealed EDC contamination in one system, at 1.25 μg/ℓ.

In the National Screening Program for Organics in Drinking Water (NSP), conducted from June 1977 to March 1981, both raw and finished drinking water samples from 169 water systems in 33 states were analyzed for 51 organic chemical contaminants (SRI, 1981). Analyses were carried out by gas chromatography with various detection methods, including the mass spectrometer, halogen-specific detector, and flame ionization detector.

Thirteen groundwater supplies were tested for EDC contamination during the NSP study. Of these systems, one was found to be contaminated with EDC at 0.2 μg/ℓ. Surface water samples for 107 drinking water systems were analyzed for EDC. Of these, only one system was found to be contaminated with EDC, at 3.8 μg/ℓ.

In the Community Water Supply Survey (CWSS), carried out in 1978, 110 surface water and 330 groundwater supplies were examined for contamination by volatile organic chemicals (U.S. EPA, 1981a). Fourteen purgeable organic compounds were analyzed, and total organic carbon levels were determined. At the time of analysis, the samples were 1 to 2 years old. Long storage periods may have resulted in the loss of some aromatics and unsaturated halocarbons due to biological action. The analytical method of choice for the CWSS was purge-and-trap gas chromatography with an electrolytic conductivity detector for halocarbons and a flame ionization detector for aromatic analysis.

The CWSS survey provided information on EDC levels in finished groundwater supplies from 312 systems. Of the samples taken from these systems, three contained detectable quantities of EDC with levels of 0.57, 1.06 and 1.1 μg/ℓ. Of the 110 surface water systems tested, only one contained quantifiable EDC, with a concentration of 0.62 μg/ℓ.

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0.5-18 µg/ℓ; the mean and median concentrations of the positive values were 5.6 and 1.7 µg/ℓ, respectively. Both the mean and median values of all samples were <0.5 µg/ℓ. Of the 47 surface water samples, only one (2.1%) was found to have EDC present (minimum quantification limit generally 0.5-1.0 µg/ℓ). The concentration of the one positive sample was 19 ug/ℓ. The mean and median values of all samples were both <0.5 µg/ℓ.

The combined EDC groundwater data and surface water data from the above Federal studies are summarized in Tables 7-3 and 7-4, respectively. The RWS study was deleted from these summarizations because the RWS data were recorded by number of service connections rather than population served. From the data presented in Tables 7-3 and 7-4, Letkiewicz et al. (1982) have projected that EDC levels in all groundwater and surface water systems in the United States fall below 10 µg/ℓ, and that most are below 1.0 µg/ℓ.

In addition to the six Federal surveys discussed by Letkiewicz et al. (1982), six states (California, Connecticut, Deleware, Indiana, Massachussetts and New Jersey) provided the U.S. EPA with information concerning EDC contamination in groundwater supplies. These data are listed in Table 7-5. The only state-supplied surface water information on EDC was from New York; one sample from Poughkeepsie assayed positive at 5.9 µg/ℓ (Letkiewicz et al., 1982).

7.1.3. Soil and Sediment Levels

No data were available on monitoring of EDC concentrations in soils, sediments or solid wastes in the sources consulted for this report.

7.2. ENVIRONMENTAL EXPOSURE

The general population can be exposed to EDC from three sources, air emissions, drinking water and consumed foods. Some individuals may be exposed to EDC from sources other than the three considered here, such as in occupational settings and in the use of consumer products containing EDC. However, this

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TABLE 7-4

Reported Occurrence of Ethylene Dichloride in Surface Water Systems -- Combined Federal Data (NORS, NOMS, NSP, CWSS)[a]

System size (population served)	Number of systems in U.S.	Number of positive systems[b] / Number of systems sampled	Positive systems (%)	Number undetected <1.0 µg/ℓ	Number of systems with measured concentration (µg/ℓ) of:			
					<1.0	1.0-5	>5-10	>10
<100	1,412	0/4	0.0	4	0	0	0	0
101-500	2,383	0/19	0.0	19	0	0	0	0
501-1,000	1,341	0/13	0.0	13	0	0	0	0
1,001-2,500	1,911	1/22	4.5	21	1	0	0	0
2,501-3,300	514	0/6	0.0	6	0	0	0	0
3,301-5,000	720	1/15	6.7	14	0	1	0	0
5,001-10,000	912	0/10	0.0	10	0	0	0	0
10,001-50,000	1,306	1/38	2.6	37	1	0	0	0
50,001-75,000	156	2/22	9.0	20	1	1	0	0
75,001-100,000	85	0/14	0.0	14	0	0	0	0
>100,000	218	5/102	4.9	97	3	1	1	0

[a] Four systems reported as undetected with the unusually high detection limit of 2.0 µg/ℓ were deleted.

[b] Positive systems are those with quantified levels of ethylene dichloride.

Source: Letkiewicz et al., 1982

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[b] Positive systems are those with quantified levels of ethylene dichloride.

Source: Letkiewicz et al., 1982

TABLE 7-5

State Data on Ethylene Dichloride in Groundwater[a]

Location	Water type	Mean (μg/ℓ)	Range (μg/ℓ)	Number of samples
CALIFORNIA				
Baldwin Park	N/S	21		1
Morada	N/S	12		1
Unspecified	N/S	1.2		2 (1 ND)
Unspecified	N/S		1.2, 5.3	2
CONNECTICUT				
Colchester	D	ND		1
Danbury	D	7.8		1
DELAWARE				
Collins Park	F	ND		1
Midvale	F	ND		1
Newark (North and South)	F	ND		2
INDIANA				
Elkhart	F, N/S	777	30-2,100	11 (4 ND)
Granger	N/S		19, 160	15 (13 ND)
MASSACHUSETTS				
Acton	F	ND		4
Belchertown	F	14.5	10.1-19.1	10 (7 ND)
Dartmouth	F		11.6, 18.2	2
Rowley	F	ND		1
NEW JERSEY				
Bergen County	N/S	ND		4
Essex County	N/S	ND		7
Fair Lawn	F, N/S	1.3	1.1-1.9	15
Morris County	N/S		2.0-2.1	13 (11 ND)
Passaic County	N/S	ND		1
9 counties	N/S	ND		154
12 counties	N/S	ND		228
	N/S		0.1-0.9	4
	N/S		1-10	4
	N/S		10-100	1

[a] Letkiewicz et al., 1982

ND = Not detected, N/S = Not specified, F = Finished, D = Distribution section is limited to air, drinking water and food since these are considered to be general sources common to most individuals. It must be noted that individual exposure will vary widely depending upon factors such as where the individual lives, works or travels, or what the individual may eat or drink. Individuals living in the same neighborhood can experience vastly different exposure patterns.

Unfortunately, methods for estimating the exposure of identifiable population subgroups from all sources simultaneously have not yet been developed (Letkiewicz et al., 1982). Exposure from the three sources considered here are discussed below.

7.2.1. Exposure from Air. Atmospheric exposure to EDC appears to vary greatly from one location to another. Mean levels as high as 27.5 ppb have been monitored near production and use facilities in Lake Charles, LA (Elfers, 1979). However, the available monitoring data (see Section 7.1) indicate that most locations have EDC concentrations of 0.5 ppb or less. The monitoring data presented are not sufficient to determine regional variations in exposure levels for EDC. The majority of high values reported were for samples taken near production and use facilities.

Letkiewicz et al. (1982) have estimated respiratory intake of ethylene dichloride by adults and infants; these estimates are summarized in Table 7-6. From available monitoring data, Letkiewicz et al. (1982) estimated that low, intermediate and high exposure levels for EDC in air were 0.25, 2.5 and 25 ug/m^3, respectively. Daily intake of EDC for adults in intermediate exposure levels was estimated at 0.82 μg/kg.

Dispersion models have also been used to estimate ambient concentrations. Based on modeled results for individual plants, maximum concentration levels in the vicinity of various emission sources have been calculated (SRI Interna-

TABLE 7-6

Estimated Respiratory Intake of Ethylene Dichloride by Adults and Infants[a]

	Exposure Level		Intake (μg/kg/day)	
	μg/m^3	(ppb)	Adult	Infant
Low:	0.25	(0.062)	0.08	0.06
Intermediate:	2.5	(0.62)	0.82	0.57
High:	25	(6.20)	8.21	5.71

Assumptions: 70 kg-man, 3.5 kg-infant, 20 m^3 of air inhaled/day (man), 0.8 m^3 of air inhaled/day (infant).

[a] Letkiewicz et al., 1982

tional, 1979). Table 7-7 shows a summary of estimated maximum concentrations that people may be exposed to in the vicinity of specific emission sources.

7.2.2. Exposure from Water. Letkiewicz et al. (1982) have projected that EDC levels in all groundwater and surface water systems in the U.S. fall below 10 µg/ℓ, and that most are below 1.0 µg/ℓ (see Section 7.1.2). The total estimated population exposed to EDC from both ground and surface water sources is shown in Table 7-8. The values in the table were obtained by use of the Federal Reporting Data System data on populations served by primary water supply systems and data on the estimated number of these water systems which contain a given level of EDC (see Section 7.1.2).

Letkiewicz et al. (1982) have also estimated daily intakes of EDC from drinking water. These estimates are given in Table 7-9.

7.2.3. Exposure from Food. EDC is used as a fumigant for grain, so contamination of flour and bread is possible. Several studies on this question have indicated that EDC dissipates when the bagged flour is exposed to air, and that no detectable EDC remains after baking (U.S. EPA, 1981b). No further information on the presence of EDC in food was uncovered in the literature search.

7.3. CONCLUSIONS

Most EDC exposures result from the production and use of the chemical. The highest atmospheric concentrations monitored for EDC have been detected near production and use facilities. Therefore, it appears that the risk for population exposure to EDC is greatest in the vicinity of these sources.

TABLE 7-7

Maximum Concentration Level in the Vicinity of Various Emission Sources[a]

Source	Maximum Annual Average EDC Concentration Level (ppb)
EDC Production Facilities	>10[b]
End Use Production Facilities	0.60 - 0.99
Gasoline Service Stations	0.01 - 0.029
Automobile Emissions	0.01 - 0.029
Automobile Refueling	<0.01

[a] SRI International, 1979

[b] An accurate estimate cannot be determined from this reference, but it is thought to be in the range of 10-15 ppb.

TABLE 7-8

Total Estimated Population (in Thousands) Exposed to Ethylene Dichloride in Drinking Water at the Indicated Concentration Ranges[a]

System type	Total served in U.S. (thousands)	Population (thousands) exposed to concentrations (μg/ℓ) of: <1.0	1.0-5	>5-10	>10
Groundwater	69,239		69,239		0.0
Surface water	126,356		126,356		0.0
TOTAL	195,595		195,595		0.0
(% of total)	(100%)		(100%)		(0.0%)

[a] Letkiewicz et al., 1982

TABLE 7-9

Estimated Drinking Water Intake of Ethylene Dichloride by Adults and Infants[a]

Exposure Level	Intake(ug/kg/day)	
	Adult	Infant
1.0	0.029	0.24
5	0.14	1.2
10	0.29	2.4
100	2.9	24.0

Assumptions: 70 kg-man, 3.5 kg-infant, 2 ℓ of water/day (man), 0.85 ℓ of water/day (infant).

[a] Letkiewicz et al., 1982

8. ECOLOGICAL EFFECTS

A variety of studies have demonstrated that EDC, in the role of a fumigant, is toxic to insects infesting stored grains (Wadhi and Soares, 1964; Ellis and Morrison, 1967; Vincent and Lindgren, 1965; Swapp, 1958; Krohne and Lingren, 1958; Finnegan and Stewart, 1962; Lindgren et al., 1954; and Berg and Telford, 1966). Little is known, however, of the effects of EDC to soil microflora.

1,2-Dichloroethane has been reported to be non-toxic to many economically important plant species when directly applied to growing plants (Gast and Early, 1956).

Toxicity of EDC to barnacles (Barnacle nauplii) and unicellular algae has been reported (Pearson and McConnell, 1975). The LC_{50} for Barnacle nauplii was reported to be 186 mg/ℓ. The effective concentration needed to reduce the photosynthetic ability of unicellular algae by 50% was 340 ppm (340 mg/ℓ).

A 24-hour median tolerance limit of 320 ppm (320 mg/ℓ) was reported for brine shrimp under static test conditions (Price and Conway, 1974).

Static 24-hour and 96-hour LC_{50} concentrations of >600 and 430 mg/ℓ, respectively, have been determined for the freshwater bluegill (Lepomis macrochirus) (Buccafusco et al., 1981). Garrett (1957) reported that the concentration of EDC needed to produce >50% mortality in the marine pinperch (Lagodon rhomboides) under static conditions was 175 mg/ℓ.

An acute LC_{50} of 115 mg/ℓ was reported for the marine flatfish (Limanda limanda) (Pearson and McConnell, 1975). In acute tests with another marine species, static 24-, 48-, 72- and 96-hour LC_{50}s in the range of 130-230 mg/ℓ were determined for sheepshead minnows (Cyprinodon variegatus) (Heitmuller et al., 1981); the observed no-effect concentration was reported to be 130 mg/ℓ. The estimated acceptable concentration of EDC in a 28-day early life stage toxicity test with freshwater fathead minnows (Pimephales promelas) lies in the range of 29-59 mg/ℓ (Benoit et al., 1982).

9. BIOLOGICAL EFFECTS IN MAN AND EXPERIMENTAL ANIMALS

9.1. PHARMACOKINETICS

9.1.1. Absorption and Distribution.

Ethylene dichloride [EDC; 1,2-dichloroethane] is a colorless, oily liquid with a sweet taste and with a chloroform-like odor detectable over a range of 6-40 ppm. It is appreciably soluble in water (0.869 g/100 mℓ) (Von Oettingen, 1964), with a vapor pressure of 64 torr at room temperature (20°C). Consequently, EDC is rapidly and extensively absorbed through the lungs in its vapor form and from the gastrointestinal tract in solution. Inhalation is considered the primary route of entrance into man from occupational exposure and air pollution. Absorption after oral ingestion is of particular interest for EDC as a contaminating component of drinking water and foodstuffs. Skin absorption is negligible in most industrial vapor exposure situations, although absorption may be significant by this route with direct liquid contact, as evidenced by toxic symptomatology in man (Section 9.2), and also quantitative animal measurements.

9.1.1.1 DERMAL ABSORPTION -- Tsuruta (1975, 1977) studied the percutaneous absorption of a series of chlorinated organic solvents (including EDC) applied to a standard area of shaved abdominal mouse skin for 15 minute periods. Absorption was quantitated by the presence of the compound in total mouse body plus expired air, as determined by gas chromatography (GC). For all solvents, percutaneous absorption linearly increased with time and the rate was directly related to water solubility. For EDC, the absorption rate was 479 nmoles/min/cm^2 skin, second highest of 8 solvents measured. Tsuruta concluded that skin absorption from liquid contact could be a significant route for EDC entry into the body.

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Jakobson et al. (1983) also carried out dermal absorption studies with guinea pigs for 10 chlorinated organic solvents including EDC. Liquid contact (skin area, 3.1 cm^2) was maintained for up to 12 hours and solvent concentration monitored in blood during and following dermal application. Dermal absorption, as reflected by blood concentration profile, was again observed to be related to the water solubility of the solvent. For solvents like EDC, which are relatively hydrophilic [300-900 mg/dl], the blood concentration increased steadily during the entire exposure. EDC reached 20 μg/mℓ blood in 12 hours. With extended dermal exposure, the blood concentration eventually became fatal. This pattern of steady blood accumulation indicates that dermal absorption occurs faster than body elimination by metabolism or pulmonary excretion. Following dermal exposure, the EDC concentration in blood declined in a manner consistent with a two-compartment kinetic model, i.e., the sum of two exponential terms.

9.1.1.2 ORAL ABSORPTION -- In man, gastrointestinal absorption of EDC has not been specifically studied, although the absorption rate after oral ingestion has been determined in animal studies. As expected from the neutral and lipophilic properties of EDC (Tables 9-1 and 9-2), transmucosal diffusive passage occurs readily. There are numerous reports of poisoning in humans as a result of accidental or suicidal ingestion of EDC and the peroral LD_{50} approximates 0.2-1 g/kg (NIOSH, 1976).

In animals, extensive gastrointestinal absorption of EDC has also been clearly demonstrated by the biological effects produced by peroral administration of a wide range of dosages and dosing schedules in toxicity studies in rats, mice, guinea pigs and dogs (Section 9.2) and in metabolism studies in rats (Reitz et al., 1980, 1982; Spreafico et al., 1978, 1979, 1980). Reitz et al. (1980, 1982) found that ^{14}C-EDC in corn oil given perorally to rats (150 mg/kg) was completely absorbed by virtue of a complete recovery of radioactivity in exhaled

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Table 9-1 Physical Properties of Ethylene Dichloride and Other Chloroethanes

		Ostwald Solubility Coeff., 37°C		
	Vapor Press. at 25°C, torr.	Water/ Air	Blood/ Air	Olive Oil/ Air
1,2-Dichloroethane	80	11.3	19.5	447
1,1-Dichloroethane	250	2.7	4.7	187
1,1,1-Trichloroethane	125	0.93	3.3	356

Adapted from Sato and Nakajima, 1979.

Table 9-2 Partition Coefficients for Ethylene Dichloride

MAN		
Blood/air, 37°C	19.5	Sato and Nakajima, 1979
Adipose tissue/blood, 25°C	56.7	Bonitenko et al., 1977
RAT, 250 ppm inhalation exposure*		
Blood/air, 37°C, 250 ppm	30.3	Spreafico et al., 1980
37°C, 150 ppm	14.9	Reitz et al., 1980
Adipose tissue/blood	8.7**	Reitz et al., 1980
Lung tissue/blood	0.45**	Reitz et al., 1980
Liver tissue/blood	0.72**	Reitz et al., 1980

*Conversion factors: At 25°C/760 torr, 1 ppm in air = 4.05 mg/m^3
1 mg/liter air = 247 ppm

**Dose-dependent

air, urine and carcass (Table 9-3). Spreafico et al. (1978, 1979, 1980) found that 25, 50 and 150 mg/kg administered orally to rats in corn oil was rapidly absorbed with peak blood levels occurring within 20 minutes. Their data, given in Figure 9-1, show the time-course of blood, liver, lung and adipose tissue following oral administration of the three dose levels. The peak blood levels, which, according to linear kinetics, should be proportional to the amount of EDC absorbed into the rat body, are summarized in Table 9-4. Although the peak blood levels in this study do not deviate drastically from linearity, the peak tissue levels are not linearly proportional to the three oral doses. These results strongly suggest a passive transport across the gastrointestinal tract of EDC and the occurrence of nonlinear elimination kinetics for EDC, i.e., a nonlinear dose-dependency related to saturation of liver metabolism of EDC. An influence of the dose on kinetic parameters has also been found for halogenated ethylene compounds (e.g., vinyl chloride, vinylidene chloride) by other investigators (Gehring et al., 1976, 1977, 1978; Bolt, 1978; McKenna et al., 1978; Reichert and Henschler, 1978; Filser and Bolt, 1979).

Table 9-5 gives the absorption rate constants (k_a) and areas under the blood concentration curves (AUC) found by Spreafico et al. (1978, 1979, 1980) for rats given a single oral dose of EDC. The rate constant for absorption was dose-dependent and was probably influenced by liver metabolism. A markedly lower value was observed for the highest dose (150 mg/kg) at which saturation of liver metabolism probably occurs. Nonetheless, these data show that EDC is absorbed from the gastrointestinal tract rapidly, with one-half the dose absorbed within 3.3 minutes for the lowest dose given in corn oil (25 mg/kg) and 6.4 minutes for the highest dose in corn oil (150 mg/kg). As expected, absorption of EDC occurred significantly faster with an oral dose in water than in oil [k_a, 0.299

Table 9-3 Fate of ^{14}C-EDC in Rats 48 Hours After Oral (150 mg/kg) or Inhalation (150 ppm, 6-hr) Exposure

	Oral		Inhalation	
	µmole/kg	% metabolites	µmole/kg	% metabolites
Body burden (total radio-activity)	1539 ± 391	-	512 ± 135 9.4 ± 0.4	-
Charcoal trap (B)	447 ± 60	-	9.4 ± 0.4	-
Total metabolites (A-B)	(1092)	(100)	(503)	(100)
Urine	926 ± 348	85.7	432 ± 121	84.4
CO_2 trap	83.1 ± 11.9	7.7	36.1 ± 6.89	7.0
Total carcass (48 hr after exposure)	46.9 ± 14.7	4.3	22.7 ± 3.38	4.4
Feces	26.3 ± 14.7	2.1	8.90 ± 2.84	1.7
Cage wash	12.5 ± 6.37	1.1	3.34 ± 1.34	0.7

Values are mean ± S.D., with n = 4 for each route of exposure and are µmole equivalents of EDC, based on the specific activity of ^{14}C-EDC (3.2 mCi/mM).

From Reitz et al., 1980.

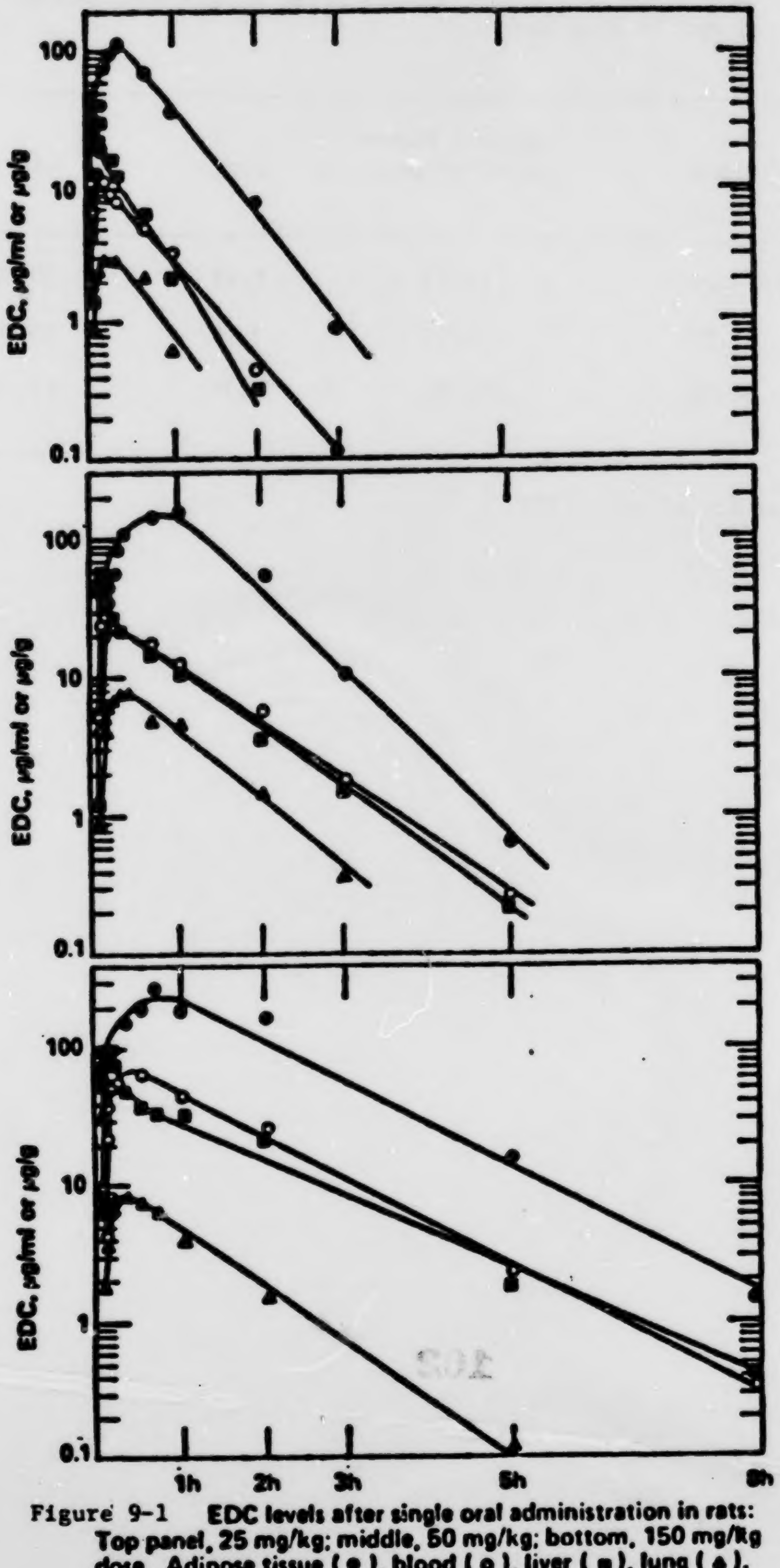


Figure 9-1 **EDC levels after single oral administration in rats: Top panel, 25 mg/kg; middle, 50 mg/kg; bottom, 150 mg/kg dose. Adipose tissue (●), blood (○), liver (■), lung (▲). Source: Spreafico et al. (1978, 1979, 1980).**

Table 9-4 Peak Blood and Tissue Levels After Single Oral Dosage of EDC in Male Rats

Dose mg/kg	Blood	Adipose tissue µg/ml or µg/g	Lung	Liver
25	13.29	110.67	2.92	30.02
50	31.94	148.92	7.20	55.00
150	66.78	259.88	8.31	92.10

Adapted from Spreafico et al., 1980

Table 9-5 The Absorption Rate Constants (k_a) and Area Under Curve (AUC) for Rats After Single Oral with Doses of EDC in Oil and in Water as Vehicle and After Intravenous Administration

	Dose (mg/kg)	k_a min^{-1}	AUC (blood) $\mu g \times \text{min} \times \text{ml}^{-1}$
Oral	25	0.299 (water) 0.209 (oil)	466 466
	50	0.185 (oil, male) 0.181 (oil, female)	1700 1685
	150	0.109 (oil)	7297
Intravenous (water)	1	-	9
	5	-	54
	25	-	595

From Spreafico, 1978, 1979, 1980

(water) vs. k_a, 0.209 (oil); 25 mg/kg]. There appears to be no gender difference for absorption.

Comparison of the area under the blood concentration curve (AUC) after intravenous administration with AUC after the same oral dose provides a measure of the extent or completeness of oral absorption. Table 9-5 shows that the AUC was 595 ug x min x $m\ell^{-1}$ after a 25 mg/kg intravenous dose and was 466 ug x min x $m\ell^{-1}$ after 25 mg/kg oral dose. These results indicate that absorption of the oral dose was very extensive, averaging 78% of complete absorption, or 100% absorption if it is assumed that the first-pass effects in liver (metabolism) and lung (elimination) after oral absorption decreased EDC appearance in systemic blood (Reitz, 1980, 1982). It is notable that the AUCs for differing intravenous doses, where intestinal absorption is not a factor (Table 9-5), are not linearly proportional, providing further evidence of the occurence of Michaelis-Menten elimination kinetics for EDC.

Withey et al. (1982) investigated the effect of the dosing vehicle on intestinal absorption of EDC in fasting rats (400 g) following intragastric intubation of equivalent doses (100 mg/kg) in ≈4 mℓ of water or of corn oil. The post-absorptive peak blood concentration averaged 5 times higher for water vehicle than corn oil (84.6 vs 15.9 ug/mℓ); moreover, the peak blood concentration was reached 3 times faster for water solution than for oil solution (3.2 vs. 10.6 minutes). The ratio of the areas under the blood concentration curves for 5 hours after dosing (AUC, 5 hr) was 3.0; water:corn oil. These results are in general agreement with those of Spreafico et al. (1978, 1979, 1980) (Tables 9-4 and 9-5), who found that intestinal absorption was faster with an oral dose in water than in oil. The observations of these investigators stress again the dependence of oral absorptive rate in rats not only on the dose, but also on the vehicle. While these factors are unlikely to affect the pharmacokinetics of EDC in man in any practical way, they are of importance to interpretation of data from long-term carcinogenicity tests of EDC in rodents where the modes of intragastric dosing employed may differ by both dose and vehicle.

9.1.1.3 PULMONARY ABSORPTION -- EDC has a moderately high vapor pressure (80 torr at 25°C; Table 9-1) and, in man, a high blood/air partition coefficient compared to chloroethanes (19.5 at 27°C; Table 9-2). Hence, its vapor in ambient air is a primary mode of exposure, and the lungs are a principal route of entry into the body. The total amount absorbed via the lungs (as for all vapors) can be expected theoretically to be directly proportional to: (1) the concentration of the inspired air; (2) the duration of exposure; (3) the blood/air Ostwald solubility coefficient; (4) the solubility in the various body tissues; and (5) physical activity which increases pulmonary ventilation rate and cardiac output. Hence, the basic kinetic parameters of pulmonary absorption of EDC and its equilibrium in the body are as valid for the very low concentrations expected in urban ambient air as for the higher vapor concentrations found in the industrial environment and the workplace. However, these parameters of pulmonary absorption have not been studied in any detail in man, although some information is available from pharmacokinetic studies in rats.

Urosova (1953) reported that women exposed during a normal day in the workplace to ≃15.5 ppm EDC in air accumulated the chemical in breast milk and that initial concentrations in exhaled air following daily exposure were 14.5 ppm. These observations indicate that the women absorbed EDC through their lungs and reached blood and total body equilibrium with inspired air concentration within the daily work period.

Spreafico et al. (1978, 1979, 1980) and Reitz et al. (1980, 1982) have studied the kinetics of pulmonary absorption of EDC in rats. Figure 9-2 shows the time-course of blood concentration of EDC, observed by Reitz et al. (1980,

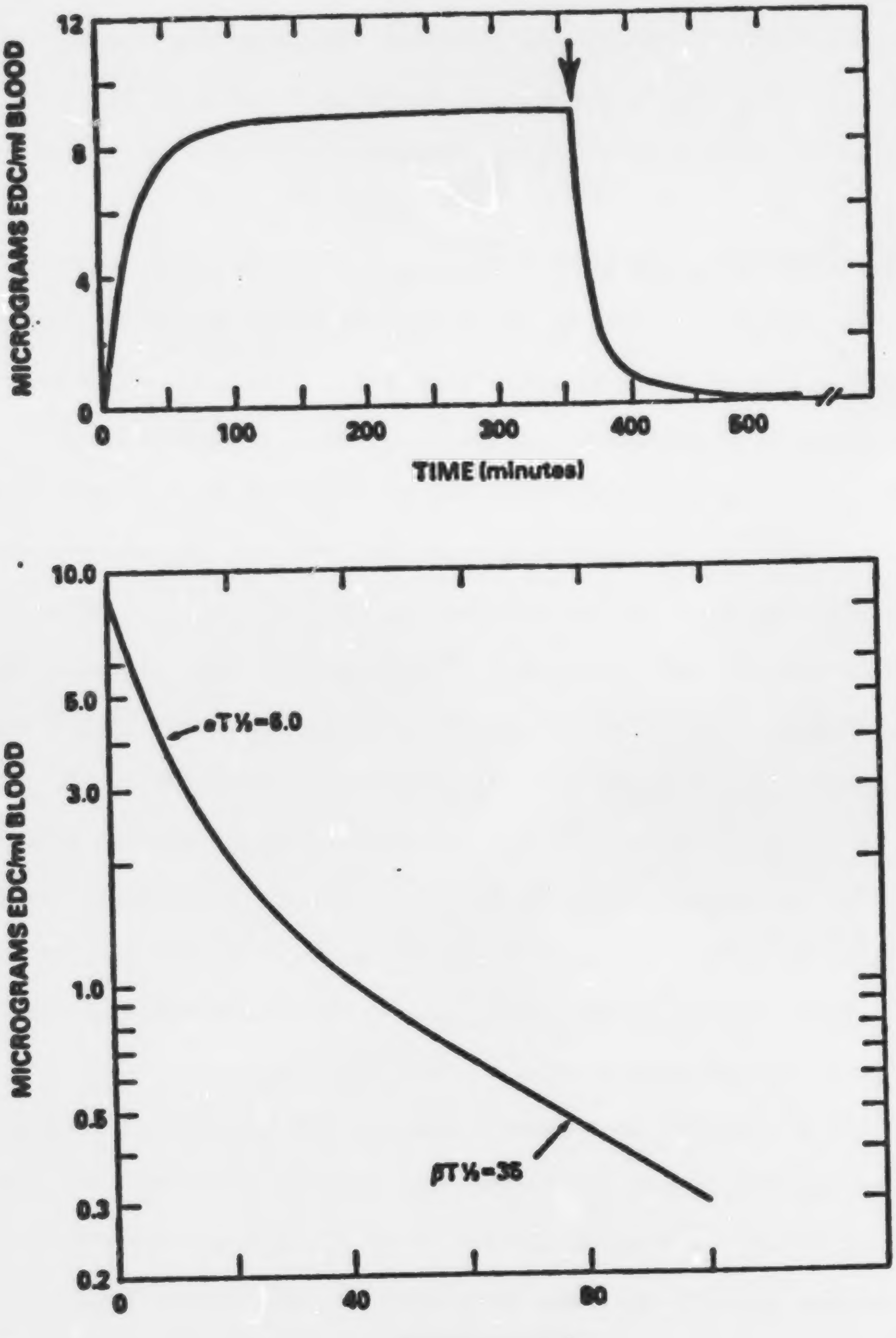


Figure 9-2 Top: Blood levels of EDC observed during and following a 6-hour inhalation exposure to 150 ppm EDC. Data from four male Osborne-Mendel rats were fitted to a two-compartment open model as described by Gehring et al.[35] The computer plot is shown. The arrow indicates exposure termination. Bottom: Semi-logarithmic plot of EDC blood levels vs. time after exposure termination. Source: Reitz et al. (1980, 1982).

1982) during a 6-hour inhalation exposure to 150 ppm EDC. Blood and body equilibrium with the blood concentration maintained a plateau level of 9 μg/mℓ (blood/air partition coefficient, 14.9). Spreafico et al. (1980) exposed their rats to 50 and 250 ppm EDC for 6 hours. Their data are given in Tables 9-6 and 9-7. Blood and body equilibrium (liver, lung and adipose tissue) was established at ≈2 hours for 50 ppm exposure, and at 3 hours for 250 ppm exposure. During inhalation of EDC, when equilibrium is achieved, the arterial blood concentration of EDC should theoretically always be directly proportional to inspired air concentration. This fixed relationship is defined by the blood/air Ostwald solubility coefficient for EDC. As calculated from the data for 50 and 250 ppm exposures of Spreafico and co-workers, the blood/air partition coefficients for EDC are 6.3 and 30.3, respectively. Including the data of Reitz et al. (1980) for 150 ppm exposure in rats (Figure 9-2), these results do not demonstrate a direct proportional relationship between inspired air concentration and blood concentration of EDC, i.e., a constant blood/air partition coefficient value. Furthermore, linear kinetics for EDC during inhalation exposure cannot be presumed, and indeed these data suggest otherwise, and are in accord with the evidence of nonlinear kinetics after oral and intravenous dosing as noted above (Table 9-5).

9.1.1.4 TISSUE DISTRIBUTION -- After pulmonary or peroral absorption, EDC is distributed into all body tissues. As expected from its general anesthetic properties in man and in animals, EDC readily passes the blood-brain barrier. The compound crosses the placental barrier and has been found in the fetus (Vozovaya, 1975, 1976, 1977). EDC also distributes into human colostrum and mature breast milk. Urusova (1953) found EDC concentrated in breast milk (5.4-6.4 mg/ℓ) in the workplace. The compound remained in breast milk for 18 hours following workday exposure, even though its concentration in exhaled air

Table 9-6 EDC Tissue Levels After 50 ppm Inhalatory Exposure

Time of Exposure	EDC µg/g or ug/ml + S.E.			
	Blood	Liver	Lung	Adipose Tissue
30 minutes	0.48 ± 0.05	0.32 ± 0.02	0.14 ± 0.02	2.91 ± 0.22
1 hour	0.92 ± 0.09	0.67 ± 0.04	0.27 ± 0.03	7.49 ± 0.60
2 hours	1.34 ± 0.09	0.84 ± 0.09	0.34 ± 0.03	10.31 ± 0.94
4 hours	1.34 ± 0.11	1.14 ± 0.17	0.42 ± 0.05	11.08 ± 0.77
6 hours	1.37 ± 0.11	1.02 ± 0.10	0.38 ± 0.02	10.19 ± 1.00

From Spreafico et al., 1980

Table 9-7 EDC Tissue Levels After 250 ppm Inhalatory Exposure

	EDC ug/g or ug/ml + S.E.			
Time of Exposure	Blood	Liver	Lung	Adipose Tissue
30 minutes	6.33 ± 1.04	3.82 ± 0.78	2.19 ± 0.21	26.75 ± 3.12
1 hour	11.65 ± 1.12	7.34 ± 0.74	6.40 ± 0.20	82.64 ± 2.19
2 hours	23.64 ± 0.91	16.39 ± 1.18	14.07 ± 0.47	151.53 ± 12.17
3 hours	29.36 ± 1.01	20.83 ± 2.21	14.47 ± 1.12	252.18 ± 14.62
6 hours	31.29 ± 1.19	22.49 ± 1.12	14.14 ± 0.90	273.32 ± 12.46

From Spreafico et al., 1980

fell to 4 ppm. Sykes and Klein (1957) have demonstrated the presence of EDC in cows' milk after oral administration.

There is little information on EDC distribution and concentration in the various body tissues of man after exposure, and few controlled exposure studies in animals investigating the distribution of EDC in body tissues and defining dose-dependent tissue concentrations. Spreafico et al. (1978, 1979, 1980) determined EDC levels in rat blood, liver, lung and epididymal adipose tissue after single oral administration of 25, 50 and 150 mg/kg. The time-course of EDC concentrations are shown in Figure 9-1. This figure shows that tissue accumulation occurs most rapidly in the liver where peak concentrations were reached within 10 minutes of administration. Following complete absorption and body equilibration after 2 hours, the decay in tissue concentrations of liver, lung and adipose tissue parallel the first-order decline in blood concentration. Table 9-8 summarizes blood and tissue concentrations determined at 2 hours following administration. Blood levels and tissue levels in liver and adipose tissues were not found to be linearly proportional to dose, but increased exponentially, providing evidence of liver metabolism saturation and nonlinear kinetics after oral administration. At oral dose levels of 25, 50 and 150 mg/kg, adipose tissue displayed the greatest concentration of EDC with adipose tissue/blood partition coefficients of 17, 9 and 7, respectively. No other tissue, including liver, demonstrated a partition coefficient >1.0. The very low concentration levels of EDC in lung tissue may occur as a result of EDC elimination by this route.

Table 9-8 also gives blood concentrations after chronic oral administration to rats (11 daily doses) of 50 mg EDC/kg. Comparison of these tissue levels with those following a single oral administration of 50 mg/kg EDC provides no evidence of blood or tissue accumulation with chronic administration.

Table 9-8 Blood and Tissue Levels of EDC in Male Rats 2 Hours After Single Oral Doses in Corn Oil

Tissue (µg/ml, or µg/g ± SE)	Dose, mg/kg		
	25	50	150
Blood	0.46 ± 0.04	5.89 ± 0.41	26.60 ± 1.23
Liver	0.32 ± 0.01	3.81 ± 0.45	21.62 ± 3.99
Kidney		3.43 ± 0.26	
Brain		2.96 ± 0.36	
Spleen		1.79 ± 0.35	
Lung	<0.05	1.44 ± 0.10	1.62 ± 0.25
Adipose	7.80 ± 0.72	55.78 ± 6.88	178.50 ± 24.66

Blood and Tissue Levels of EDC in Male Rats 2 Hours After the Last of 11 Daily Oral Doses in Oil (50 mg/kg)

Blood		8.11 ± 0.23	
Liver		3.95 ± 0.48	
Lung		2.24 ± 0.47	
Adipose		53.71 ± 10.07	

From Spreafico et al., 1978, 1979, 1980.

Spreafico and his colleagues (1978, 1979, 1980) also investigated blood and tissue concentrations in rats during inhalation exposure to 50 and 250 ppm EDC. The results of these experiments are given in Tables 9-6 and 9-7. Blood and tissue equilibrium (liver, lung and adipose tissue) occurred at 2 hours and 3 hours, respectively, for the two inspired air concentrations. In general, the blood and tissue distribution of EDC at body equilibrium is similar to the results obtained with oral administration given in Table 9-8. A very clear dose dependence in tissue levels of EDC was again found with the two inhalation concentrations, with differences in EDC concentrations on the order of 20-30 times when blood, liver, lung and adipose tissue are considered. The highest absolute levels of EDC were measured again in adipose tissue with concentrations that were between 8 and 9 times greater than those measured in the blood. As previously noted for oral administration (Table 9-8), liver and lung concentrations were less than blood concentrations.

A comparison of the absolute blood and tissue concentrations at body equilibrium for oral and inhalatory modes of administration (Tables 9-6, 9-7 and 9-8) indicates that 50 ppm inhalation roughly equates to 25 mg/kg oral, while 250 ppm inhalation provides blood, liver and adipose tissue levels slightly greater than a 150 mg/kg oral dose.

9.1.2 Excretion. Elimination of EDC from the body is perforce the sum of metabolism and excretion of unchanged EDC via pulmonary and other routes. Unmetabolized EDC is excreted almost exclusively through the lungs; however, metabolism of EDC is extensive, with the proportion excreted unchanged dependent on body doses. While no controlled experimental studies have been made on the kinetics of excretion of EDC in man, recent studies have been performed on experimental animals.

9.1.2.1 PULMONARY EXCRETION -- Urusova (1953) reported that women exposed to ≃15.5 ppm EDC in ambient air of industrial environs demonstrated initial EDC concentrations in exhaled air of 14.5 ppm. The breath concentration declined to ≃3 ppm after 18 hours. These values lead to an approximation of 9 hours for the half-time of pulmonary elimination of EDC in man. Similar observations have been made for animals (monkey, dog, cat, rabbit, rat and guinea pig) in early investigations of the anesthetic properties and toxicities of EDC (Heppel et al., 1945; Kistler and Luckhardt, 1929; Lehman and Schmidt-Kehl, 1936). In controlled studies in mice, Yllner (1971a) found that up to 45% of an intraperitoneal injected dose of EDC (170 mg/kg) was recoverable unchanged in exhaled air (Table 9-9). The percentage of EDC recovered unchanged in exhaled air increased exponentially with the dose, indicating a limited capacity of biotransformation, i.e., non-linear kinetics. Thus, in mice, pulmonary excretion of EDC is a major route of elimination, increasing in importance with higher body doses.

Similar observations have been made for the rat by Reitz et al. (1980, 1982). In a balance study utilizing ^{14}C-EDC given orally (150 mg/kg) and by inhalation (150 ppm, 6 hours), these investigators found that for the oral dose, 29% was recovered unchanged in exhaled air, and that only 1.8% of the lower inhalation dose was excreted by the pulmonary route (see Table 9-3). Sopikov and Gorshunova (1979) observed that after an intraperitoneal 250 mg/kg dose to rats, 30% of the EDC dose was eliminated in the exhaled air within 5 hours.

9.1.2.2 OTHER ROUTES OF EXCRETION -- EDC is not ordinarily eliminated in significant amounts from the body by any route other than pulmonary. However, Shchepotin and Bondarenko (1978) identified EDC by gas chromatography (GC) methods in the urine of persons with severe symptoms of EDC poisoning. Studies of chlorinated compounds in the urine after EDC inhalation exposure or peroral dosage to experimental animals have failed to detect unchanged EDC (Spreafico et

Table 9-9 Percent Distribution of Radioactivity Excreted (48-hr) by Mice Receiving 1,2-Dichloroethane-^{14}C

	Dose g/kg			
	0.05	0.10	0.14	0.17
$^{14}CO_2$ (exhaled air)	13	8	4	5
Dichloroethane (exhaled air)	11	21	46	45
Urinary metabolites	73	70	48	50

Adapted from Yllner (1971a)

al., 1980; Yllner, 1971a). Mutagenic metabolites of EDC have been reported in rat and mouse bile (Rannug and Beije, 1979; Rannug, 1980), but EDC itself has not been found. Diffusion of volatile haloalkane anesthetic agents into bowel space and through skin is known to occur (Stoelting and Eger, 1969), and these routes of excretion may also be significant for EDC because of similarity of structure and comparable high lipid/blood partition coefficients.

9.1.2.3 KINETICS OF EXCRETION -- While the kinetic parameters of elimination of EDC for each of the various routes of excretion, i.e., pulmonary, metabolism, etc., are not well defined for either man or experimental animals, several investigative groups have determined the kinetic parameters for whole-body and tissue compartment excretion of EDC in the rat (Retiz et al., 1980; Spreafico et al., 1978, 1979, 1980; Withey and Collins, 1980).

Withey and Collins (1980) determined the kinetics of distribution and elimination of EDC from blood of Wistar rats after intravenous administration of 3, 6, 9, 12 or 15 mg/kg of EDC given in 1 mℓ water intrajugularly. For the two lower doses (3 and 6 mg/kg), the blood decay curves exhibited two components of exponential disappearance and best fitted a first-order two compartment model with kinetic parameters of: k_e, 0.24 min^{-1}; V_d, 43 mℓ; k_{12} and k_{21}, 0.02 and 0.04 min^{-1}, respectively. For higher doses (9, 10 and 15 mg/kg), these investigators found their data best fitted a first-order three compartment model; they suggest that the shift from two to three compartment kinetics may have occurred either because of a dose-related alteration in the kinetic mechanisms of uptake, distribution, metabolism and elimination, or that three compartment kinetics were followed at all dose levels but with lower doses; the third exponential component, representing the third compartment, was obscured by the limit of analytical sensitivity. Average kinetic values for the three compartment model were: k_e, 0.094 min^{-1}; V_d, 67.9 mℓ; k_{12}, k_{21}, k_{13}, k_{31}; 0.06, 0.08, 0.01 and 0.01 min^{-1}, respectively. Withey and Collins state that they found no evidence in their kinetic analysis of the disposition of intravenous bolus injections of EDC into the rat of nonlinear or dose-dependent Michaelis-Menten kinetics. These workers suggested that a dose of 15 mg/kg EDC in the rat is below hepatic metabolism saturation.

Spreafico et al. (1978, 1979, 1980) intravenously administered EDC in water to Sprague-Dawley rats as bolus injections of 1, 5 and 25 mg/kg and determined the whole blood concentration of EDC as it decayed with time. Figure 9-3 shows the semilog plot of the results of these experiments. A biphasic decline of EDC blood concentration was evident for all doses, indicative of a two-compartment system, with a distributive phase (α) and an excretion phase (β). The data for intravenous treatment were analyzed by computer fitting to a two-compartment open model with the results shown in Table 9-10. Of immediate note is the fact that the kinetic parameters are not independent of the dose as required by linear kinetics. Thus the half-time ($T_{1/2}$) of body elimination from central or blood compartment increases with the dose, while whole-body clearance (Cl) and the volume of distribution (V_d) decrease with an increase of the dose. These results indicate that the rate of whole-body excretion of EDC is largely determined by the metabolism of EDC, a saturable process and a major route of elimination.

Spreafico and his co-workers (1978, 1979, 1980) have also investigated the whole-body kinetics of oral administration of EDC in rats. Figure 9-1 shows semilog plots of blood and tissue concentrations during and after absorption (excretory phase) following single oral doses of 25, 50 and 150 mg/kg given in corn oil. In general, the slopes of the disappearance curves (excretion component) for adipose, liver and lung tissues roughly parallel and reflect the blood decay curve. The data for blood were computer-fitted to the kinetic equations

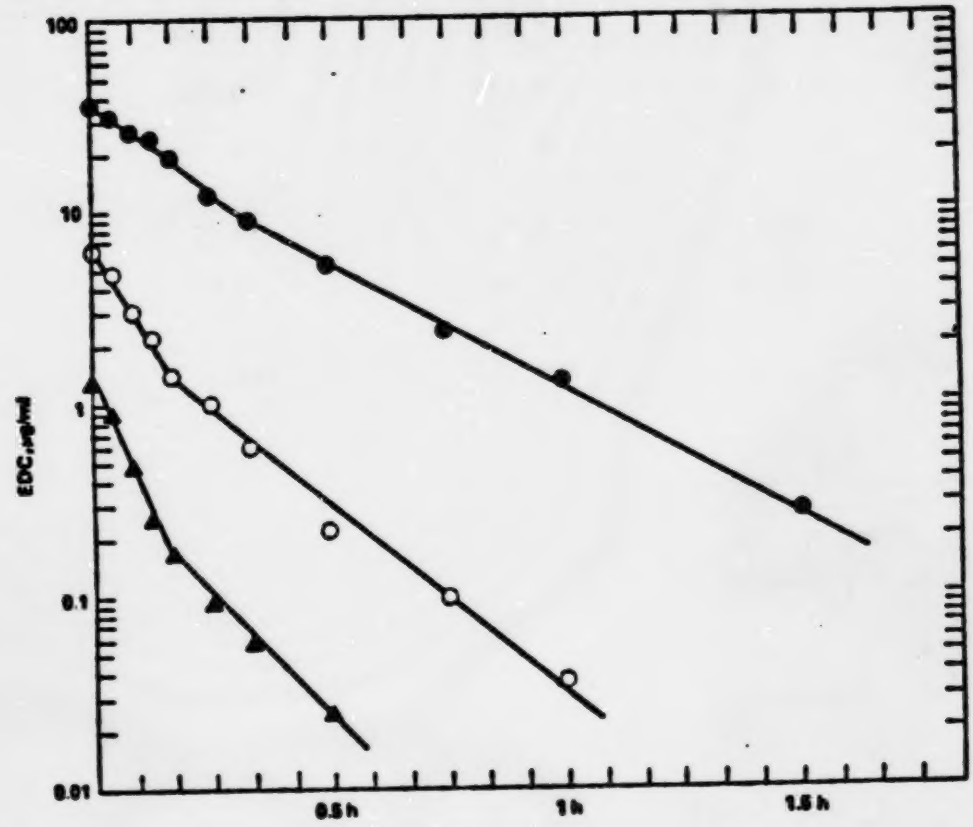
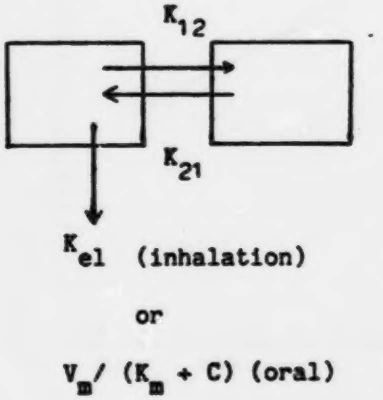


Figure 9-3 Blood levels of EDC in rats after i.v. administration. (●) 25 mg/kg i.v.; (○) 5 mg/kg i.v.; (▲) 1 mg/kg i.v. Source: Spreafico et al. (1978, 1979, 1980).

Table 9-10 Pharmacokinetic Parameters of EDC Administered as Single Bolus Intravenous Injections in Saline to Sprague-Dawley Male Rats. Parameters Calculated from a 2-Compartment Open Model.

Parameter	Dose, mg/kg 1	 5	 25
C_o, µg x ml^{-1}	1.50	8.00	38.12
K_{el}, min^{-1}	0.277	0.142	0.078
K_{12}, min^{-1}	0.121	0.063	0.040
K_{21}, min^{-1}	0.158	0.140	0.118
AUC, µg x min x ml^{-1}	9	54	595
T 1/2 β min	7.30	9.49	14.07
Clearance ml x m^{-1}	21.98	17.46	7.98
Vol. distr., ml	231	239	162



From Spreafico et al., 1979, 1980.

for a two-compartment open model for oral absorption; the results are given in Table 9-11. Like the kinetics observed for intravenous dosing, the values for the parameters, $T_{1/2}$, Cl and V_d, are dose-dependent. Furthermore, the oral dosing vehicle also affects the parameters. Comparison of the absorption rate constants, K_a, half-times of elimination, $T_{1/2}$ and volumes of distribution, V_d, for 15 mg/kg EDC in oil and 25 mg/kg EDC in water indicates a faster absorption of EDC in water, a shorter half-time of body elimination and a small volume of distribution. Nonetheless, the AUCs indicative of the total absorbed dose were similar for oil and water vehicles, as were the body clearance rates of EDC. On the other hand, no significant differences in the kinetic parameters were seen for male and female rats given the same dose, nor were significant differences observed between a single dose and 11 daily administrations of the same dose (50 mg/kg) of EDC.

Spreafico et al. included in their comprehensive studies on the pharmacokinetics of EDC in the rat, experiments to determine the kinetics of EDC after inhalation dosing. Rats were exposed to 50 and 250 ppm EDC for 5 hours, a period sufficiently long to estabish and maintain whole body steady-state conditions with these inspired air concentrations (Tables 9-6 and 9-7). The exposure was terminated and blood and other tissues were sampled to determine the decay of EDC concentrations in these tissues with time. The results of these experiments are presented as semilog plots of tissue concentrations versus time in Figure 9-4. As for oral dosing, the slopes of the tissue decay curves parallel and reflect generally the blood concentration curves. In contrast to intravenous and oral dosing, which have several components to their curves representing absorption and/or distribution, the curves after steady-state inhalation are monophasic, representing only excretion. Thus, the pharmacokinetic parameters calculated from the blood decay curves following the steady-state inhalation conditions are

Table 9-11 Pharmacokinetic Parameters of EDC Administered as Single Oral Doses in Corn Oil and Water to Sprague-Dawley Male Rats. Parameters Calculated from a 2-Compartment Open Model.

Parameter	Dose, mg/kg 25	 50	 150
Oil Vehicle			
K_a, min^{-1}	0.209	0.185	0.109
K_{el}, min^{-1}	0.029	0.017	0.010
AUC, ug x min x ml^{-1}	446	1700	7297
T 1/2 β min	24.62	44.07	56.70
Clearance, ml x min^{-1}	10.64	5.58	3.90
Vol. Distr., ml.	367	328	390
Aqueous Vehicle			
K_a, min^{-1}	0.299		
K_{el}, min^{-1}	0.046		
AUC, ug x min x ml^{-1}	446		
T 1/2 β min	14.12		
Clearance, ml x min^{-1}	10.20		
Vol. Distr., ml.	221		

From Spreafico et al., 1979, 1980.

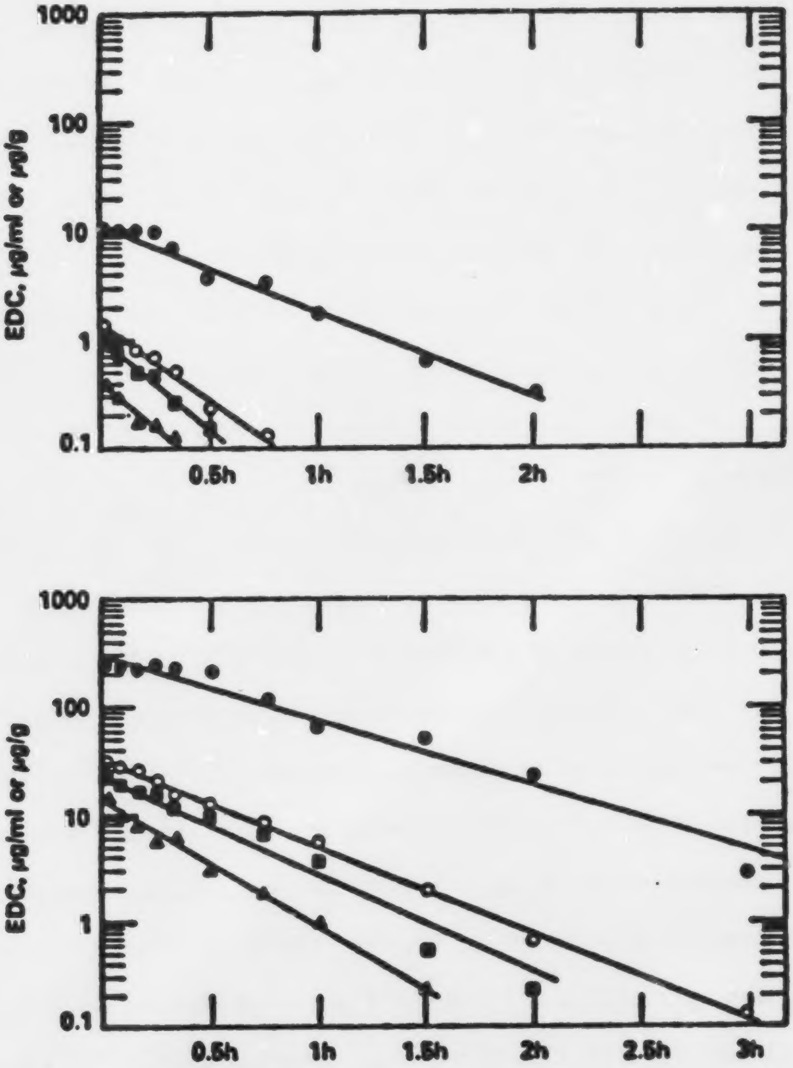


Figure 9-4 **Levels of EDC in rats after inhalatory exposure to 50 ppm (top) and 250 ppm (bottom). Levels were measured at termination of 5-hour exposure period. Adipose tissue (●), blood (○), liver (■), lung (▲). Source: Spreafico et al. (1978, 1979, 1980).**

essentially those applicable to a single compartment open model. The kinetic parameters are given in Table 9-12. The body burden or "dose" of EDC in the animals at termination of inhalation exposure is not known; however, a comparison of the areas under the blood decay curves, a reflection of body burden, suggests that the body burden after 250 ppm exposure was 40 times, not the 5 times expected of the 50 ppm exposure. Similarly, the half-life of EDC and the zero-time blood concentrations are dose-dependent. These results from inhalation exposure are in accord with the dose-dependent pharmacokinetics exhibited after intravenous and oral dosing of EDC. They strongly indicate that the kinetics of absorption, distribution and elimination of EDC are appropriately described by nonlinear kinetics that take into account saturable processes, presumably in this case the metabolism of EDC by the organism.

The pharmacokinetics of EDC after inhalation have also been explored by Reitz et al. (1980, 1982) in male Osborne-Mendel rats. These investigators determined the whole-blood levels of EDC during and following a 6-hour inhalation exposure to 150 ppm EDC. Figure 9-2 shows the data obtained from 4 rats, computer-fitted to the equations of a two-compartment model and the idealized computer-fit plotted. Within 2 hours of exposure, the animals approached a steady-state blood concentration (9 μg/mℓ) with the inspired air concentration; but, following termination of exposure at 6 hours, the blood concentration of EDC rapidly decayed to near zero within 10 hours. Figure 9-2 shows also the semilog plot of computer-fitted data of EDC blood concentration levels vs. time after exposure termination. In contrast to the observation of Spreafico et al. (Figure 9-4) that only a monophasic plot was obtained following inhalation exposure, Reitz et al. found a biphasic elimination with an initial rapid alpha phase and a slower beta phase. Table 9-13 gives the pharmacokinetic parameters calculated

Table 9-12 Pharmacokinetic Parameters of EDC Following Termination of Steady State Inhalation Conditions (5-hr Exposure) of 50 and 250 ppm to Male Sprague-Dawley Rats.

Parameter	Exposure Concentration, ppm 50	 350
C_o, $\mu g \times ml^{-1}$	1.42	30.92
K_{el}, min^{-1}	0.0561	0.0313
T 1/2, min	12.69	22.13
AUC, $\mu g \times min \times ml^{-1}$	26	1023

From Spreafico et al., 1979, 1980

Table 9-13 Pharmacokinetic Parameters of EDC Following Termination of Steady State Inhalation Conditions; 6-Hr Exposure, 150 ppm to Male Osborne-Mendel Rats. Parameters Calculated from a 2-Compartment Model.

Parameter	
C_o, µg x ml^{-1}	9.0
K_{el}, min^{-1}	0.092
K_{12}, min^{-1}	0.019
K_{21}, min^{-1}	0.025
AUC, µg x min x ml^{-1}	3018
$T_{1/2\beta}$ min	35
Vol. Distr, ml.	513

From Reitz et al., 1980

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from a two-compartment open model. These results may be compared with data obtained by Spreafico et al. for inhalation exposure (Table 9-12).

Reitz et al. (1982) determined also in the rat the pharmacokinetics after single oral dosing (150 mg/kg in corn oil). In this case, a semilog plot of blood EDC levels after absorption produced an elimination curve typical of nonlinear kinetics. These workers therefore computer-fitted the data to a two-compartment nonlinear model and calculated the rate of elimination from the central compartment (blood) according to Michaelis-Menten kinetics. Table 9-13 gives the pharmacokinetic parameters calculated from the model.

Several differences exist between the observed data and calculated parameters of Reitz et al. for inhalation vs. oral exposure (Table 9-13) as well as those of Spreafico et al. (Table 9-12). The EDC inhalation concentration used by Reitz et al. (150 ppm) was intermediate to those of Spreafico et al. (50 and 250 ppm). Plateau blood concentrations in the three inhalation studies (1.4 at 50; 8.3 at 150; and 30.9 µg/mℓ at 250 ppm), clearly demonstrate saturation of an elimination process, presumably metabolism. Reitz et al. found peak blood levels following oral dosing (30-44 µg/mℓ at 150 mg/kg) to be similar to those found by Spreafico et al. after a 250 ppm inhalation exposure. Reitz et al. found also a biphasic elimination after both oral and inhalation exposure with the second or β phase essentially equal ($T_{1/2}$ = 28 min), and similar to the monophasic elimination calculated by Spreafico et al. for the 250 ppm exposure ($T_{1/2}$ = 22 min). The relatively slow alpha elimination phase ($T_{1/2}$, 90 min) following oral dosing of 150 mg/kg suggested to Reitz et al. a saturable elimination process. The data of Spreafico and co-workers are generally in agreement with this treatment; however, several kinetic parameters are not in good agreement between the studies. Of particular note are the biphasic and monophasic elimination curves and the large discrepancy of AUC. The explanation for these differences may lie in the different kinetic models, species differences and inability of linear kinetics to accurately describe the kinetics of EDC body elimination.

9.1.2.4 BIOACCUMULATION -- There is no definitive experimental evidence in the literature concerning bioaccumulation in man after chronic or repeated daily exposure to EDC. While EDC has a moderately high fat tissue/blood partition coefficient (Table 9-2), its half-time of elimination in man appears to be ≈6-8 hours (Urusova, 1953). In the rat, Spreafico et al. (1978, 1979, 1980) and Retiz et al. (1980, 1982) have provided estimates of half-time of whole-body elimination of 25-57 minutes for acute oral dosing, and 13-35 minutes after 5-6 hour inhalation exposures. The half-time of elimination of EDC from the epididymal adipose tissue was essentially the same as whole-body elimination. These relatively short half-times of elimination indicate that the risk of significant bioaccumulation of EDC is small. These investigators observed also that their pharmacokinetic data in rats predict essentially complete elimination of EDC from the body in 24 hours following acute oral or 5-6 hour inhalation exposure. Furthermore, Spreafico et al. (1979, 1980) found no significant differences in the kinetic parameters of EDC elimination between a single dose and multiple daily oral administration of EDC.

9.1.3. Metabolism

9.1.3.1 KNOWN METABOLITES -- Metabolism of EDC in man during or after exposure has not been studied. However, one of the earliest suggestive reports of an active mammalian biotransformation of EDC is related to human exposure. In 1945, Bryzkin reported that EDC underwent rapid transformation to an "organic chloride" in patients who died after ingesting 150-200 mℓ; EDC itself was not detectable in tissues at autopsy. Although Heppel and Porterfield demonstrated as early as 1948 that both ethylene dichloride and dibromide were dehalogenated by rat liver enzyme preparations, current knowledge of mammalian metabolism of

EDC derives primarily from studies performed within the last 10 years. Metabolites which have been identified either in vivo in mice and rats or in liver and kidney tissue crude enzyme systems are listed in Table 9-14. In addition to the very active metabolite, 2-haloacetaldehyde, other possible reactive intermediates formed during the metabolism of 1,2-dihaloethylenes by glutathione-dependent reactions, such as an episulfonium ion, may be involved in the covalent binding to tissue macromolecules leading to tissue damage (Rannug and Beije, 1979; Hill et al., 1978; McCann et al., 1975; Guengerich et al., 1980; Anders and Livesey, 1980).

9.1.3.2 MAGNITUDE OF EDC METABOLISM -- The capacity of mammalian organisms to metabolize EDC has been studied only in the mouse and rat. In these two species, the extent of biotransformation of single doses of EDC has been estimated by balance studies utilizing ^{14}C-EDC.

Yllner (1971a) administered intraperitoneally doses of 50-170 mg/kg of ^{14}C-EDC to mice in metabolism units with CO_2 and solvent traps. Yllner recovered 97-100% of radioactivity in exhaled air and urine within 24 hours. The results of his balance studies are summarized in Table 9-9. For the low dose of 50 mg/kg, Yllner found that 86% was metabolized to CO_2 (13%) and water and to other metabolites appearing in the urine (73%). Unchanged EDC did not appear in the urine, but 11% of the dose was eliminated unchanged in exhaled air. An increase of the intraperitoneal dose resulted in a smaller percentage of the dose being metabolized. For the largest dose, 170 mg/kg, 55% was metabolized to CO_2 (5%) and urine metabolites (50%). These results indicate that extensive biotransformation (55-86%) occurs in the mouse. Furthermore, the extent of metabolism is dose-dependent, suggesting a limited capacity for biotransformation with saturation of the metabolizing system(s). Saturation of metabolism to CO_2 and urinary

Table 9-14 Identified Metabolites of Ethylene Dichloride and Ethylene Bromide.

	System	Reference
Inorganic halide	rat liver cytosol	Heppel and Porterfield, 1948 Nachtomi, 1970
CO_2	mouse, rat exhaled air	Yllner, 1971b Reitz et al., 1980
2-Chloroethanol	mouse, rat urine, blood	Yllner, 1971b Kokarovtseva and Kiseleva, 1978
2-Chloroacetic acid	mouse urine	Yllner, 1971b
Bromoacetaldehyde	rat liver microsomes	Hill et al., 1978
Thiodiglycolic acid	mouse, rat urine	Yllner, 1971b Spreafico et al., 1979
Ethylene	rat liver cytosol	Livesey and Anders, 1979
S-(2-hydroxyethyl)-cysteine	rat liver cytosol, rat urine	Nachtomi et al., 1966 Edwards et al., 1970
N-acetyl-S-(2-hydroxyethyl)-cysteine	rat urine	Edwards et al., 1970
N-acetyl-S-(2-hydroxyethyl)-oxide	blood	
S-carboxymethyl cysteine	mouse urine	Yllner, 1971b
S-(2-hydroxyethyl)-glutathione S-(2-hydroxyethyl)-S-oxide	rat liver cytosol, tissue	Nachtomi, 1970
S,S'-ethylene-bis-glutathione	rat liver	Nachtomi, 1970

metabolites occurred at a dose level of between 100-140 mg/kg and 50-100 mg/kg, respectively.

Reitz et al. (1980, 1982) have found that EDC is also extensively metabolized in the rat. These investigators conducted balance studies with ^{14}C-EDC in Osborne-Mendel rats after oral (150 mg/kg) and inhalation (150 ppm for 6 hours) exposure. Their results are summarized in Table 9-3. In the oral balance study, 150 mg/kg of ^{14}C-EDC (or, 1520 μmoles/kg) were administered. The sum of radioactivity recovered in exhaled air, urine and feces, and that remaining in the carcass was 101% or complete recovery. Some 29% of the dose was excreted unchanged in exhaled air; 5% was metabolized completely to $^{14}CO_2$ and 60% of the dose was metabolized to ^{14}C-metabolites appearing in the urine. Less than 3% radioactivity remained in the body 48 hours after dosing (probably as covalently bound metabolites). These results indicate that the extent of total metabolism of the oral dose was ≈70% in these rats. For the inhalation exposure study, the absolute dose administered by a 150 ppm, 6-hr exposure was unknown. From the recovery after termination of exposure of ^{14}C-radioactivity in exhaled air, urine and feces, and radioactivity remaining in the carcass 48 hours after exposure, it was estimated that the inhalation dose was 50.5 mg/kg (512 μmoles/kg) or one-third of the oral dose. Of this dose, 2% was excreted unchanged in exhaled air, 7% was metabolized completely to $^{14}CO_2$, and 84% was metabolized to ^{14}C-metabolites appearing in the urine. Less than 5% of the radioactivity was left in the body 48 hours after inhalation exposure. Ignoring the pharmacokinetic differences between acute oral and inhalation dosing, the results of Reitz et al. demonstrate extensive biotransformation in the rat (70-91%) and also suggest a dose dependency with greater metabolism for lower doses, as Yllner (1971a) observed in the mouse.

The balance studies of both Yllner (oral dosing) and Reitz et al. (oral and inhalation dosing) demonstrate that the primary route of elimination of EDC is by metabolism. Renal excretion of nonvolatile metabolites predominates; however, 5-10% is metabolized completely to CO_2 and water. It is of interest to note that a small amount of EDC or its metabolites appear in the feces (<2%), even from inhalation exposure. Yllner (1971a) identified the metabolites appearing in the urine of mice after dosing with ^{14}C-EDC (170 mg/kg) and found six ^{14}C-metabolites; the three principal metabolites were: S-carboxymethylcysteine (45%), thiodiacetic acid (33%) and chloroacetic acid (15%) (Table 9-15). However, Spreafico et al. (1979) dosed rats with 50 and 150 mg/kg ^{14}C-EDC and found the principal metabolite to be thiodiacetic acid; chloroacetic acid was not detected and S-carboxymethylcysteine was found only in trace amounts.

9.1.3.3 PATHWAYS OF METABOLISM -- A number of studies have been carried out describing the metabolism of 1,2-dihaloalkanes. Two principal pathways, involving microsomal and cystosolic enzymes, respectively, have been proposed. These pathways account for the formation of the metabolites identified in both in vivo and in vitro studies listed in Table 9-14 and also suggest the nature of the reactive intermediates involved in the covalent binding to cellular macromolecules (protein and DNA) which has been demonstrated in both in vivo and in vitro studies (Section 9.1.3.5).

A. Microsomal Reactions: Yllner (1971a) originally proposed that the degradation of 1,2-dichloroethane to 2-chloroacetic acid involved a primary reaction in which chlorine was removed from one of the carbon atoms (hydrolytic dehalogenation) to yield 2-chloroethanol. As evidence for this reaction, he found chloroethanol to be a minor metabolite in the urine of mice injected with EDC (Table 9-15). Following 2-chloroethanol formation, Yllner proposed that alcohol was enzymatically converted to 2-chloroacetic acid (a major urinary

Table 9-15 Percent Distribution of Radioactivity Excreted (48-hr) as Urinary Metabolites by Mice Receiving 1,2-Dichloroethane-^{14}C or 2-Chloroacetic Acid-^{14}C.

Metabolite	After dichloroethane (0.17 g/kg)	After chloroacetate (0.10 g/kg)
Chloroacetic acid	16	13
2-chloroethanol	0.3	--
S-carboxymethylcysteine	45	39
Conjugated S-carboxymethyl-cysteine	3	3
Thiodiacetic acid	33	37
S,S-ethylene-bis-cysteine	0.9	--
Glycolic acid	--	4
Oxalic acid	--	0.2

Adapted from Yllner (1971a,b)

metabolite) via 2-chloroacetaldehyde. Kokarovtseva and Kiseleva (1978) have also identified chloroethanol in the blood of rats ($T_{1/2}$ ca. 9 hours), and in rat liver tissue within 1 hour and for 24-48 hours after oral administration of EDC (750 mg/kg). Van Dyke and Wineman (1971) and subsequently Salmon et al. (1978, 1981) found that rat microsomal fractions, in the presence of O_2 and NADPH, dechlorinated a series of haloalkanes including EDC. The reaction for EDC had a V_{max} of 0.24 nmol/min/mg protein with a K_m of 0.14 mM (Salmon et al., 1981). Thus, EDC and other haloalkanes interact with cytochrome P-450 to give a Type I difference spectra associated with the metabolism of these substrates by direct C-hydroxylation (Ivanetick et al., 1978). Besides EDC, Ivanetick et al. (1978) observed that chloroacetaldehyde and chloroethanol also interacted with cytochrome P450 with K_s values of 10.3, 30 and ≃15, respectively. Hill et al. (1978) reported that 1,2-dibromoethane was activated to an irreversibly-bound species by microsomal mixed-function oxidases, and also provided evidence that 2-bromoacetyaldehyde was formed in such reactions. More recently, Guengerich et al. (1980) showed that 2-chloroethanol was a product of rat microsomal mixed-function oxidation of EDC, requiring O_2 and NADPH. The reaction was blocked by classic P450 inhibitors and increased by pre-treatment with phenobarbital. Guengerich et al. (1980) proposed that part of the microsomal mixed-function oxidative metabolism of EDC proceeded from oxygen insertion into a C-H bond to form an unstable chlorohydrin which spontaneously dehydrohalogenates to form 2-chloroacetaldehyde. Figure 9-5 illustrates the proposed reaction and pathway. Chloroacetaldehyde is then reduced to chloroethanol by alcohol dehydrogenase in the presence of NADH, or oxidized to 2-chloroacetic acid by aldehyde dehydrogenase. Johnson (1967) previously had observed that chloroethanol was readily dehydrogenated to chloroacetaldehyde by alcohol dehydrogenases from yeast or horse liver. The reaction, therefore, proceeds in either direction depending on

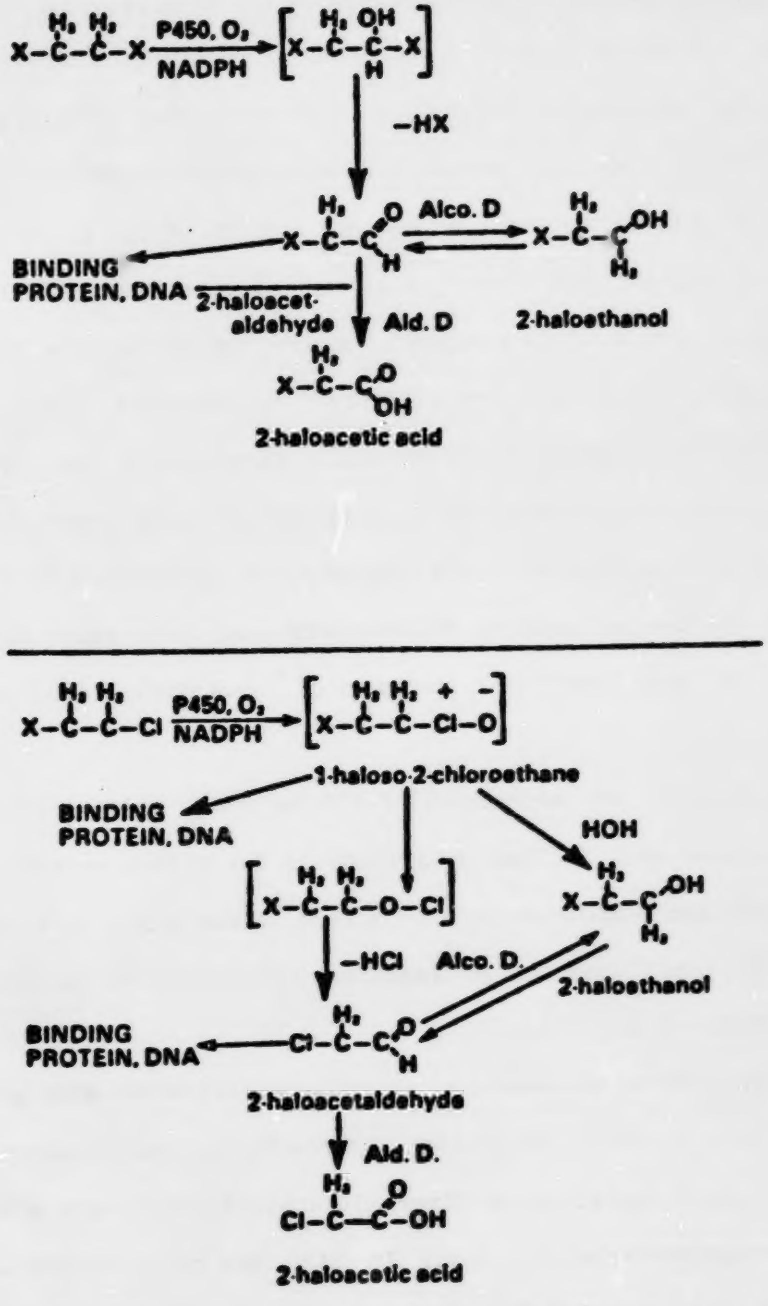

P450, O₂
NADPH
−HX
Alco. D
BINDING
PROTEIN, DNA
2-haloacetaldehyde
Ald. D
2-haloethanol
2-haloacetic acid
P450, O₂
NADPH
1-haloso-2-chloroethane
BINDING
PROTEIN, DNA
HOH
−HCl
Alco. D.
2-haloethanol
BINDING
PROTEIN, DNA
2-haloacetaldehyde
Ald. D.
2-haloacetic acid

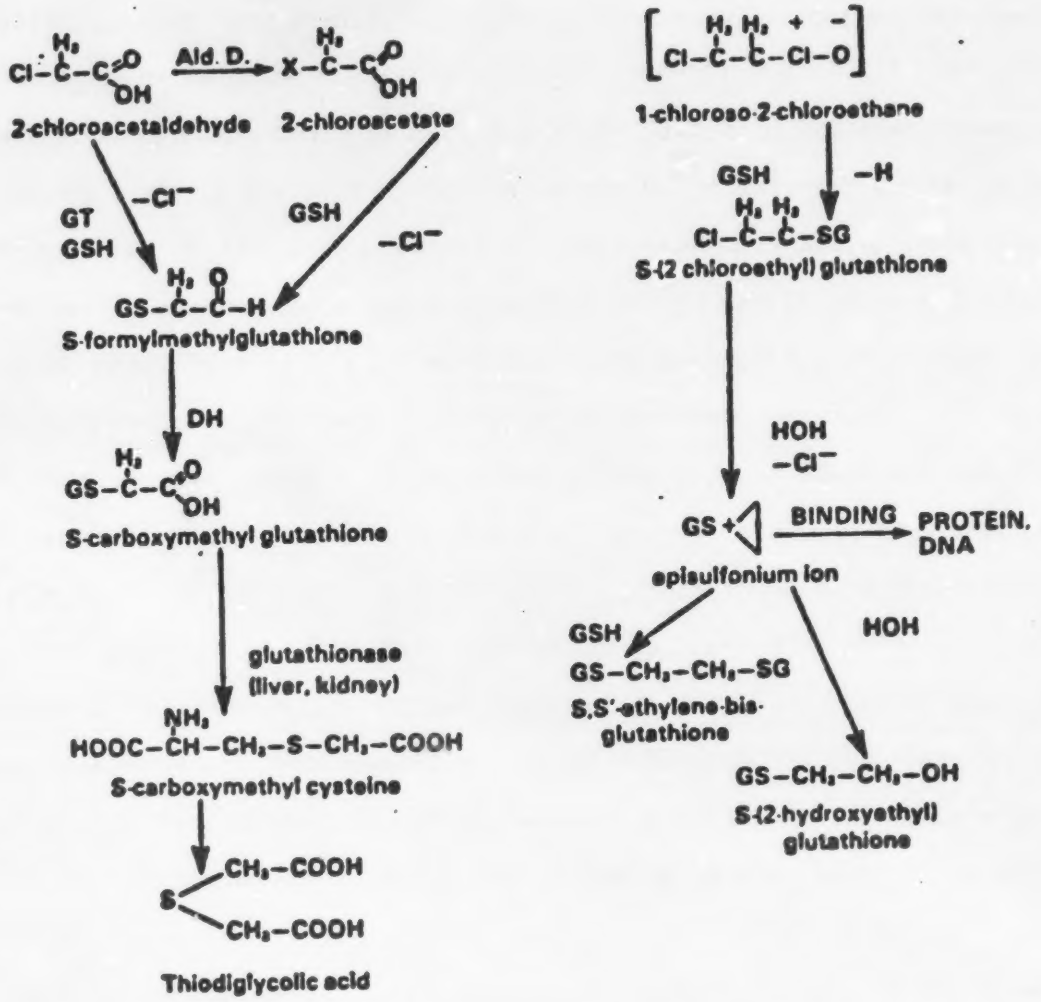
Figure 9-5 Microsomal oxidative metabolism of 1,2-dihaloethanes. Source: Adapted from Guengerich et al. (1980), Anders and Livesey (1980).

enzyme, substrate and cofactor concentrations. Williams (1959) also had suggested that chloracetic acid appeared *in vivo* via chloroacetaldehyde.

Further evidence for this reaction sequence has been provided by Guengerich et al. (1980). These workers observed that covalent binding to microsomal protein and DNA was inhibited 30-40% by inclusion of alcohol or aldehyde dehydrogenases in the reaction mixture, strongly indicating that chloroacetaldehyde was the reactive intermediate responsible for this portion of the total irreversible binding of EDC. Chloroethanol itself, when added to the microsomal system, gave only a low level of irreversible binding. In order to account for the remainder of the microsomal mixed-function oxidative irreversible binding of EDC, Guengerich et al. (1980) proposed the oxidative formation of the reactive metabolite 1-chloroso-2-chloroethane, which spontaneously rearranges to 1-chloroacetaldehyde via a hypochlorite. The reaction is illustrated in Figure 9-5. These workers noted that a reactive chloroso compound could react directly with macromolecules, or hydrolyze (with release of hypochlorite ion) to form 2-chloroethanol.

As a consequence of microsomal P-450-mediated oxidation of EDC as illustrated in Figure 9-5, further metabolism of the oxidative metabolites, 2-chloroacetaldehyde and 1-chloroso-2-chloroethane, leads either to a "detoxification" or to a further formation of reactive intermediates, respectively, as illustrated in Figure 9-6.

Regarding detoxification reactions of chloroacetaldehyde with glutathione, Johnson (1955, 1966a,b, 1967) found that chloroethanol, administered orally to the rat, caused rapid depletion of liver glutathione (GSH) with a concomitant formation of S-carboxymethylglutathione. *In vitro*, the reaction with a rat liver cytosol fraction required stoichiometric amounts of GSH (1 mole) and NAD (2 moles). Since pyruvate was also required for reaction, Johnson (1967) postulated


2-chloroacetaldehyde
Ald. D.
2-chloroacetate
GT
GSH
−Cl⁻
GSH
−Cl⁻
S-formylmethylglutathione
DH
S-carboxymethyl glutathione
glutathionase
(liver, kidney)
HOOC−CH−CH₂−S−CH₂−COOH
S-carboxymethyl cysteine
Thiodiglycolic acid
1-chloroso-2-chloroethane
GSH
−H
S-(2 chloroethyl) glutathione
HOH
−Cl⁻
BINDING
PROTEIN, DNA
episulfonium ion
GSH
HOH
GS−CH₂−CH₂−SG
S,S'-ethylene-bis-glutathione
GS−CH₂−CH₂−OH
S-(2-hydroxyethyl) glutathione

GSH, glutathione; Ald. D, aldehyde dehydrogenase; GT, GSH tranferase; DH, dehydrogenase

Figure 9-6 . Further metabolism of 2-chloroacetaldehyde and 1-chloroso-2-chloroethane from microsomal oxidation. Source: Adapted from Guengerich et al. (1980) and Anders and Livesey (1980).

that chloroethanol was converted by alcohol dehydrogenase to chloroacetaldehyde, which then conjugated with GSH to give S-formylmethylglutathione, and thence by an NAD requiring dehydrogenation to S-carboxymethylglutathione. Johnson (1966b) reported that chloroacetaldehyde also rapidly conjugates with GSH in vitro by a non-enzymatic reaction at pH 7.0. He also has shown that S-carboxymethylglutathione is rapidly degraded by rat kidney homogenate to yield glycine, glutamic acid and S-carboxymethylcysteine, part of which is further metabolized to thiodiglycolic acid. Yllner (1971a) found that these latter two metabolites were the two major urinary compounds after administering EDC to mice (Table 9-15). Since these two compounds were also the major urinary metabolites after administering 2-chloroacetate to mice (Table 9-15), Yllner (1971b) proposed that 2-chloroacetic acid could also conjugate with GSH with chloride excision forming S-carboxymethylcysteine and thereby enter the pathway (Figure 9-6). Spreafico et al. (1979) found that after rats were given oral doses of 50 and 150 mg/kg EDC, 2-chloroacetic acid did not appear in the urine, but thiodiglycolic acid did appear as the major urinary product. The difference between the urinary metabolites found in mice by Yllner and those observed in rats by Spreafico et al. may be explained by the availability of GSH in the livers of the animals in the two studies.

Reactions of putative 1-chloroso-2-chloroethane: Guengerich et al. (1980) noted that the chloroso compound which they proposed was formed by microsomal P450 oxidative emtabolism of EDC, would be extremely reactive and could be expected to either rearrange to 2-chloroacetaldehyde, hydrolyze to 2-chloroethanol, or react directly with microsomal protein (Fig. 9-5). In addition, these workers postulated that the chloroso compound may react with GSH to form S-(2-chloroethyl)glutathione, a half sulfur mustard, which could react via an episulfonium ion intermediate with macromolecules (Fig. 9-6). However, in an

Ames test with S. typhimurium TA1535, EDC activated with rat liver microsomes, NADPH, O_2 and added GSH, did not enhance mutagenic activity. In contrast, the use of 100,000 g liver supernatant containing GSH and GSH transferases markedly increased the number of revertants per 1,2-dichloroethane plate. These results suggested that either the putative chloroso compound is not formed in the microsomal system, or that differences in the subcellular systems contribute to differences in covalent binding and mutagenicity.

B. Cytosolic reactions: Heppel and Porterfield (1948) obtained an enzyme preparation from rat liver capable of hydrolyzing the carbon-halogen bonds of chloro derivatives of methane and ethane, including EDC. Bray et al. (1952) also studied the dehalogenation of dichloroethane and other halogenated hydrocarbons by rabbit liver extracts and nonenzymatic dechlorination by direct interaction with sulfhydryl groups of GSH and cysteine. Nachtomi et al. (1966, 1970), found that an enzyme system from the soluble supernatant fraction of rat liver catalyzed a reaction between EDC and GSH. The formation of inorganic halide in these studies could occur as a consequence of attack by GSH resulting in the excision of halide, and the formation of S-(2-haloethyl)-GSH (Fig. 9-7). This metabolite is a reactive intermediate, a half sulfur mustard, which, via its episulfonium ion and further reaction with a second GSH or with water, may be expected to form S,S-ethylene-bis-GSH or S-(2-hydroxyethyl)-GSH. The S,S'-ethylene-bis-GSH may be presumed to be subject to degradation to S,S-ethylene-bis-cysteine by glutathione in liver and kidney. Yllner (1971a,b) found small amounts of S,S'-ethylene-bis-cysteine in the urine of mice injected with EDC (Table 9-15). Nachtomi et al. (1970) found that the products of the soluble fraction of rat liver reaction with EDC were S,S'-ethylene-bis-glutathione and S-(1-hydroxyethyl)glutathione. Nachtomi et al. (1970) identified the same two compounds plus the sulfoxides of the former in urine of EDC- and dibromoethane-

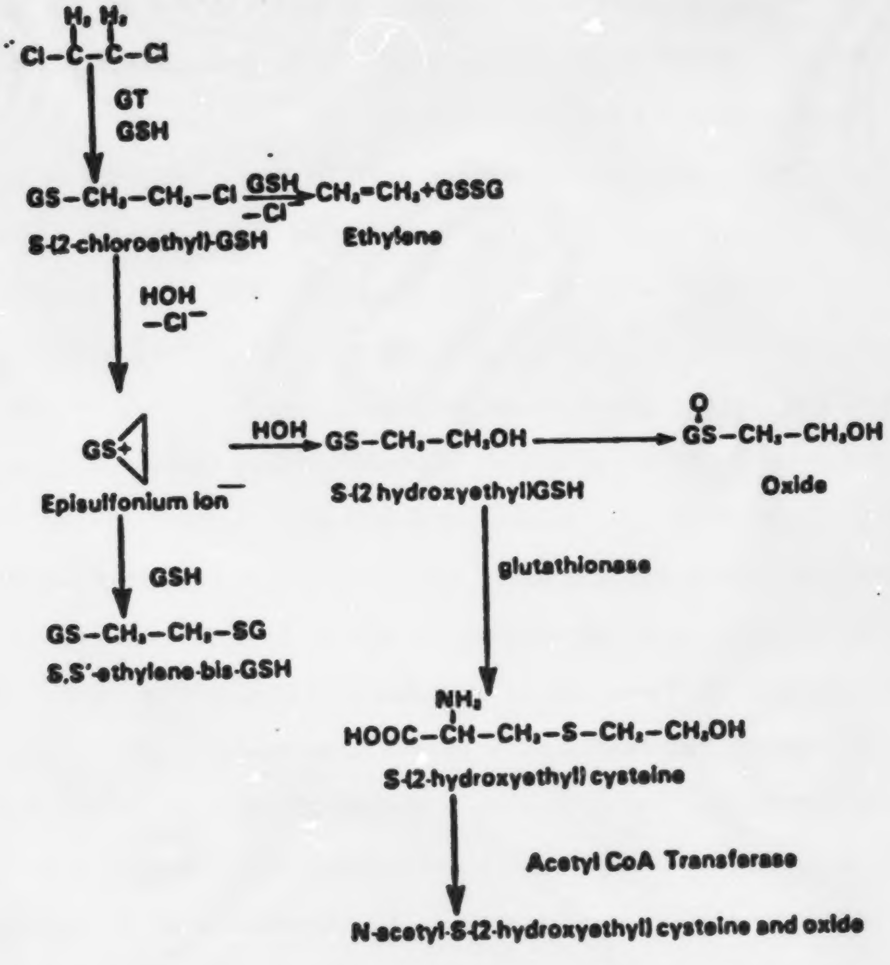

Cl–C–C–Cl
GT
GSH
GS–CH₂–CH₂–Cl
GSH
–Cl⁻
CH₂=CH₂+GSSG
S-(2-chloroethyl)-GSH
Ethylene
HOH
–Cl⁻
GS+
HOH
GS–CH₂–CH₂OH
GS–CH₂–CH₂OH
Episulfonium ion⁻
S-(2 hydroxyethyl)GSH
Oxide
GSH
glutathionase
GS–CH₂–CH₂–SG
S,S'-ethylene-bis-GSH
NH₂
HOOC–CH–CH₂–S–CH₂–CH₂OH
S-(2-hydroxyethyl) cysteine
Acetyl CoA Transferase
N-acetyl-S-(2-hydroxyethyl) cysteine and oxide

Figure 9-7 . Cytosolic metabolism of ethylene dichloride. Source: Adapted from Anders and Livesey (1980).

treated rats. Nachtomi et al. (1966) have also identified N-acetyl-S-(2-hydroxyethyl)cysteine in the urine of EDC- and 1,2-dibromoethane-treated rats. Jones and Edwards (1968) and Edwards et al. (1970) confirmed the work of Nachtomi with dibromoethane, and moreover, isolated the sulfoxides of both S-(2-hydroxyethyl)cysteine and its mercapturic acid from the urine of dibromoethane-treated rats.

The half sulfur mustard, S-(2-chloroethyl)-GSH, and its episulfonium ion formed by cytosolic GSH-dependent transferase metabolism (Fig. 9-7) has been suggested by Rannug et al. (1978, 1979, 1980) to be responsible for the mutagenic action of EDC in S. typhimurium TA1535. These workers found that activation of EDC occurred only with the soluble fraction of rat liver homogenates or with purified GSH transferase enzyme in the presence of GSH. Their findings have been confirmed by Guengerich et al. (1980). In addition, Rannug and co-workers demonstrated that S-(1-chloroethyl)cysteine and N-acetyl-S-(2-chloroethyl)-cysteine produced direct mutagenic effects when tested on Salmonella, whereas S-(2-hydroxethyl)cysteine showed no mutagenic effect. These results showed that the enzymatic degradation of the GSH moiety does not abolish the mutagenic properties of the conjugate, whereas a substitution of the chlorine with a hydroxyl group does.

C. Formation of ethylene: Livesey and Anders (1979) have identified ethylene in rat liver and kidney cytosol incubated with EDC. Ethylene was produced in only small amounts which were, however, linearly independent on the cytosolic protein concentration. The enzymatic conversion was glutathione dependent and specific for this thiol. Studies of substrate specificity with 1,2-dihaloethanes showed that reactivity following the halide order with C-Br bond cleavage and elimination occurring at a faster rate than C-Cl bond breakage. Whereas EDC conversion was primarily an enzymatic reaction, ethylene formation occurred equally well from 1,2-dibromoethane by a nonenzymatic reaction with GSH. The microsomal P-450 inhibitor, SKF 525-A, had no effect on EDC metabolism, but the reaction was inhibited by p-chloromercuribenzoic acid, methyl iodide and diethylmaleate. Livesey and Anders proposed that the intermediate in the conversion of EDC to ethylene was S-(2-chloroethyl)glutathione (Fig. 9-7). An analog of this intermediate, S-(2-chloroethyl) cysteine, was nonenzymatically converted to ethylene in the presence of glutathione and other thiols.

D. Oxidation of EDC to CO_2: After oral dosing of ^{14}C-EDC, Yllner (1971a) in the mouse and Reitz et al. (1982) in the rat found that 5-10% of the dose was metabolized completely to CO_2 and water. Yllner (1971b) also observed that after 2-chloroacetate administration, small amounts of glycolic and oxalic acids appeared in urine (Table 9-15). Since these acids are known to be metabolized to CO_2, Yllner proposed that 2-chloroacetate, arising from EDC metabolism (Fig. 9-5) is enzymatically hydrolyzed to glycolate by dehydrohalogenation, a portion of which is further oxidized to oxalic acid.

E. Comparison of the metabolism of EDC to vinyl chloride: Rannug and Beije (1979) have drawn attention to the similarities in the biotransformation pathways of EDC and vinyl chloride. For both metabolisms, S-(2-chloroethyl)-cysteine, thiodiglycolic acid, S-(2-hydroxyethyl)cysteine and its mercapturic are involved as end products. Guengerich et al. (1980) considered the possibility that reductive dechlorination of EDC would yield chloride ion plus a chloroethyl radical, which could either react with macromolecular targets, or lose a hydrogen atom to form vinyl chloride. Alternatively, some other dehydrohalogenation mechanism (-HCl) could give rise to vinyl chloride. Vinyl chloride could then be microsomally oxidized to 1-chloroethylene oxide, which can either react with macromolecules, or be rearranged to 2-chloroacetaldehyde and proceed through the pathway of Figure 9-6. However, Guengerich et al. found that reductive dechlorination of EDC to a chloroethyl radical was an unlikely reaction because metabolism and binding of EDC was dependent upon the presence of O_2 in microsomal incubations containing NADPH. Guengerich et al. calculated that the rate of EDC conversion to either a total nonvolatile or to an irreversibly bound metabolite was ≈25-50 times too high to support an obligatory role for vinyl chloride as an intermediate. Moreover, they found that irreversible binding of label from vinyl chloride to microsomal protein was inhibited 95% by either alcohol or aldehyde dehydrogenase in microsomal incubations while these conditions produced only 30-40% inhibition of binding for EDC. These investigators concluded that the metabolism of EDC probably does not involve vinyl chloride as an intermediate.

9.1.3.4 METABOLISM, TOXICITY AND MODIFIERS -- Dichloroethane metabolites, chloroacetaldehyde, chloroethanol (oral LD_{50} for rats, 96 mg/kg), and chloroacetic acid (oral LD_{50} for rats, 76 mg/kg) are several times more toxic than EDC itself (oral LD_{50} for rats, 770 mg/kg) (Heppel et al., 1945, 1946; Woodward et al., 1941; Ambrose, 1950; Hayes et al., 1973). Since the symptoms of poisoning from both accidental and occupational exposures of humans and experimental exposures of animals to these metabolites are very similar to those resulting from EDC, it can be assumed that the toxicity of EDC for both man and animals is in large part the result of biotransformation to these metabolites. Johnson (1967) was the first to suggest that chloroacetaldehyde may be the premier toxic metabolite, since this very reactive compound is capable of both enzymatic and non-enzymatic interaction with cellular sulfhydryl groups (Fig. 9-6). However, Yllner (1971a,b) found that chloroacetic acid also reacted extensively with sulfhydryl compounds _in vivo_.

Heppel et al. (1945, 1946, 1947) found a high mortality (35%) in rats given 1.3 g/kg EDC orally. Mortality was reduced by pre- or post-administration of methionine, cysteine and other sulfhydryl compounds. Sulfur-containing amino acids, cysteine and methionine, also protected young rats from inhalation exposure. This protective effect of sulfhydryl compounds is clearly related to the marked depletion of glutathione levels which occurs in the livers of rats given EDC, chloroethanol or chloroacetaldehyde (Johnson, 1965, 1966, 1967) and to the enzyme pathways of metabolism of EDC (Figs. 9-5 to 9-7). Johnson (1965, 1967) has noted that the morbidity and mortality of young rats given chloroethanol orally was reduced by concomitant administration of ethanol. He postulated that the protective effect of ethanol was due to simple substrate competition for alcohol dehydrogenase which catalyzes the conversion of chloroethanol to chloroacetaldehyde (Fig. 9-5). Ethanol also inhibited early effects of chloroethanol on liver glutathione depletion in these animals. This author also suggested that the minimal toxicity observed with chronic low inhalation doses of EDC in different animal species may be simply explained by the rapid replenishment of tissue glutathione.

Similar observations on the relation of the level of glutathione in liver and other tissues, and toxicity of the chlorocarbons, have been made by Jaeger and his co-workers (1974, 1979). Like EDC, vinylidene chloride is detoxified by glutathione-dependent pathways. Jaeger et al. (1974) found in rats that an 18-hour overnight fast decreased the LC_{50} from a 4-hour inhalation concentration of vinylidene chloride from 15,000 ppm (fed) to 600 ppm (fasted) and decreased the concentration of vinylidene chloride that produced a significant plasma elevation of α-ketoglutarate transaminase, evidence of liver cytoxicity (2000 ppm, fed; 150 ppm, fasted). Increased susceptibility to hepatotoxicity was shown to be related to a decreased hepatic glutathione concentration associated with the fasting. Jaeger (1979) also demonstrated in rats a circadian rhythm for tissue glutathione concentration of liver, blood, lung and kidney. For rats maintained on a 12-hour light-dark cycle (6 pm to 6 am, dark), hepatic glutathione content was lowest at 6-10 pm and highest at 4-12 am; these periods correspond to the greater and lesser hepatotoxicity respectively associated with vinylidene chloride exposure during these two periods.

Nakajima and Sato (1979) studied the metabolism of the chlorocarbons *in vitro* with microsomes from livers of fed and fasted male rats and found that the metabolism of EDC increased 1.5-fold as the result of a 24-hour fast, although fasting produced no significant increase in the microsomal protein and cytochrome P-450 liver contents. Microsomes from livers of fasted female rats displayed even more active metabolism of EDC (3.6-fold over fed rats). These observations suggest that the increased toxicity of EDC that occurs with food deprivation may be due not only to decreased liver glutathione content, but also to a greater production of toxic metabolites: chloroacetaldehyde, chloroethanol and chloroacetic acid.

Sato et al. (1980) have studied the effect of chronic ethanol consumption on hepatic metabolism of chlorinated hydrocarbons in rats to provide information on the effect of ethanol consumption on the toxic effects of chlorinated hydrocarbons in the work environment. Male rats were maintained on a daily intake of ethanol amounting to 30% of their total energy intake for 3 weeks. The hepatic microsomal metabolism of EDC was increased 5.5-fold over microsomes from livers of ethanol-free rats, although ethanol feeding produced only a slight increase in the microsomal P-450 content. The increase in enzyme metabolism of EDC occurred only with microsomal fractions and not with cytosolic fractions, and one day withdrawal of ethanol feeding almost completely abolished the effect of chronic alcohol consumption.

Sato et al. (1981) studied also the effects of an acute single dose of ethanol (given as an aqueous solution by gastric intubation) on the metabolism of chlorinated hydrocarbons in rats. Hepatic metabolism of EDC (by a 10,000 g liver fraction) added in vitro was accelerated (up to 2.5-fold) by doses of ethanol up to 4 mg/kg without causing any increase in P-450 content. The stimulation was not seen and even suppression occurred with higher doses of ethanol. Increased metabolism was most marked 16-18 hours after ethanol administration. Ethanol added directly to the incubation mixture, however, depressed EDC metabolism. These investigators suggest that ethanol is capable of exerting a dual effect on EDC-metabolizing enzymes, i.e., inhibition and stimulation, depending on ethanol concentration.

9.1.3.5 METABOLISM AND COVALENT BINDING -- The metabolism of EDC results in the production of reactive metabolites of an electrophilic nature such as those proposed to be formed in the metabolic schemes of Figures 9-5 to 9-7. The occurrence of these metabolites, chloroacetaldehyde, the putative 1-chloroso-2-chloroethane, the half-mustard S-(2-chloroethyl)glutathione and its episulfonium ion, provides a theoretical basis for the covalent binding observed with EDC to cellular macromolecules such as protein and DNA with consequent possibility of damage to cellular integrity and genetic apparatus. Such covalent binding reactions are known to be related to teratogenesis, mutagenesis and carcinogenesis, although chemical reactivity alone is not evidence of genetic damage (Lutz, 1979). The amount of covalent binding, and hence damage potential, is related to the pharmacokinetics of EDC exposure. At least in the rat, there is ample evidence from pharmacokinetic studies of EDC that the metabolic capacity for EDC metabolism is saturable (Sections 9.1.2 and 9.1.3). It may therefore be speculated that the organism when confronted with low quantities of EDC utilizes glutathione conjugation detoxification reactions (Fig. 9-6) and nonelectrophilic metabolites are primarily produced, but when confronted with higher EDC doses, increasing amounts of electrophilic metabolites are produced to a saturating and limiting rate for their enzymatic pathways (Figs. 9-6 and 9-7). Reitz et al.

(1980, 1982) determined total covalent binding and binding to DNA in rats exposed to ^{14}C-EDC by the oral (150 mg/kg) and inhalation (150 ppm, 6 hour) routes. The results of their study with these presumably saturating doses are given in Table 9-16. These results show no striking difference between the two routes of exposure in the distribution of covalent binding and DNA binding among the various organ tissues, although the tissue levels of covalent binding are generally higher after inhalation exposure for total binding and after gavage exposure for DNA binding. The exposure doses used in these studies of Reitz et al. are comparable to the oral doses of EDC use in the lifetime NCI carcinogenicity study (NCI, 1978) and to the inhalation doses of the carcinogenicity studies in rats of Maltoni et al. (1980). No excess tumors were reported by Maltoni et al., while liver and forestomach were sites of malignant tumors in the NCI study. Recently, Storer et al. (1982) determined DNA damage produced in vivo in the livers of male B6C3F1 mice following single oral doses of EDC (100 mg/kg). DNA damage was evaluated by sedimentation of liver nuclei in alkaline sucrose density centrifugation, and by DNA recovery. Nuclei from EDC-treated mice isolated 4 hours after dosing sedimented more slowly and the total DNA recovery was decreased 16% from untreated mice. However, dimethyl nitrosamine, used as a positive control, decreased recovery of DNA 61%.

In contrast to the low covalent binding potential of EDC in vivo, inhalation exposure of rats to only 20 ppm, 1,2-dibromoethane (EDB; 7 hours/day, 5 days/week for 18 months) produced tumors in the liver and kidney, sites of covalent binding (Hill et al., 1978). Furthermore, Plotnick et al. (1980) found that the carcinogenicity of EDB was enhanced by the dietary addition of disulfiram (0.05% by weight; an inhibitor of aldehyde dehydrogenase) which blocks the further oxidation of bromoacetaldehyde formed in the metabolism of EDB (Fig. 9-5) and which presumably results in increased tissue levels of bromoacetaldehyde with an

TABLE 9-16

Total Macromolecular Binding and DNA Binding in Selected Tissues of Rats After Exposure to ^{14}C-EDC by Oral or Inhalation Routes[b].

	Nanomole equivalents EDC/g tissue	
	oral (150 mg/kg)	inhalation (150 ppm 6 hr)
Total Binding (n=4)		
Liver[a]	175 ± 24	268 ± 45
Kidney	183 ± 25	263 ± 48
Spleen[a]	65 ± 21	130 ± 22
Lung	106 ± 34	147 ± 16
Forestomach[a]	160 ± 19	71 ± 19
Stomach	90 ± 2	156 ± 29
DNA Binding (n=3)		
Experiment 1		
Liver[a]	21.3 ± 7.4	8.2 ± 3.3
Spleen[a]	5.8 ± 0.7	1.8 ± 0.3
Kidney	17.4 ± 2.3	5.2 ± 3.7
Stomach	14.9	2.8
Experiment 2		
Liver[a]	13.9 ± 2.1	3.3 ± 1.2
Spleen[a]	2.5 ± 0.3	1.8 ± 0.5
Kidney	14.5 ± 6.2	2.0 ± 0.3
Stomach	6.7	1.9

Results are reported as nanomole equivalents of EDC/g tissue ± S.D. Animals were sacrificed 4 hr after oral dosing or immediately following a 6-hr inhalation exposure.

[a] Site where malignant tumors were observed in the NCI study (1978) after EDC was given by gavage, also forestomach. No excess tumors were reported in the inhalation carcinogenicity bioassay (Maltoni et al., 1980).

[b] Reitz et al., 1982.

increase of covalent binding. Plotnick et al. (1980) showed that dietary disulfiram markedly increased covalent binding of ^{14}C-EDB in the nuclei of liver cells in rats dosed with EDB (Table 9-17).

Covalent binding of metabolites from both oxidative microsomal and cytosolic metabolism of EDC has been demonstrated in vitro by several investigative groups. Van Duuren and his colleagues (Banerjee et al., 1978, 1979a,b, 1980) observed microsomal-activated covalent binding of both EDC and EDB to native DNA from salmon sperm, and to liver and lung microsomal protein from rats and mice. Binding to DNA did not occur in the absence of microsomes or in the presence of denatured microsomes. Cytosolic metabolism produced insignificant metabolic activation and binding. The microsomal-activated binding was enhanced by phenobarbital and 3-methylcholanthrene pretreatment, whereas the addition of glutathione to the microsomal reaction reduced the binding. Similar results were obtained by Sipes and Gandolfi (1980). Van Duuren and his co-workers suggested that EDC and EDB were biotransformed by microsomal oxidative reactions to the reactive transient metabolites, 2-haloacetaldehyde, 2-haloethanol or haloethylene oxide, all of which are electrophilic in nature. Banerjee, Van Duuren and Kline (1979b) demonstrated that both 2-bromoacetaldehyde and 2-bromoethanol bind covalently to protein and DNA without metabolic activation. Guengerich et al. (1980) have found that ^{14}C-EDC is metabolized by both microsomes and cytosolic systems to metabolites that covalently bind to protein and calf thymus DNA. Cytosolic metabolism depended upon the presence of glutathione and involved glutathione transferases (Fig. 9-7), although glutathione inhibited microsomal-activated binding to protein but stimulated binding to DNA. These investigators also produced evidence that 2-chloroacetaldehyde, S-(2-chloroethyl)glutathione, and their putative 1-chloroso-2-chloroethane are the metabolites involved in the covalent binding

Table 9-17 Effect of Dietary Disulfiram Upon the ^{14}C Content of Liver Nuclei Isolated 24 or 48 Hours After Administration of a Single Oral Dose of 15 mg/mg [U-^{14}C]EDB

Time Interval	Control	Disulfiram
24 hours	687 ± 82*	1773 ± 314
48 hours	460 ± 42	1534 ± 197

*Results are expressed as dpm/pellet (mean ± S.E.M.) of duplicate determinations on 6 animals per group at 24-hr and 5 animals per group at 48 hr.

From Plotnick et al., 1980.

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9.1.4. Summary and Conclusions. At ambient temperatures, EDC is a volatile liquid with appreciable solubility in water, and hence the principal routes of entry to the body are by pulmonary and oral absorption. The pharmacokinetics of absorption and excretion of EDC have been studied extensively in the mouse and rat. Absorption from the gastrointestinal tract is rapid and complete, occurring by first order passive processes with a half-time of <6 min. A dose-dependent first-pass effect with pulmonary elimination of unchanged EDC occurs with oral ingestion, thus decreasing the amount reaching the systemic circulation. At the low concentration of EDC existent in food and water, nearly complete extraction by the liver is expected. With inhalation exposure, a blood/air partition coefficient of ≈20 at 37°C has been observed. Tissue distribution of EDC is consistent with its lipophilic nature. The chemical crosses the blood brain and placental barriers and distributes into breast milk. The adipose tissue/blood partition coefficient varies from 7-57 depending on dose.

Excretion of unmetabolized EDC is almost exclusively via the lungs; however, metabolism and excretion of the metabolites by other routes is extensive and dose-related. In the mouse and rat, after both oral and inhalation exposure, the half-life of EDC in blood increases with dose, although it is <60 min at high doses. The parameters of total body elimination are compatible with a 2-compartment system and Michaelis-Menten kinetics. The short half-life of EDC suggests that the risk of bioaccumulation from intermittent multiple oral and inhalation exposures is small. Daily oral dosing of rats does not result in significant bioaccumulation in blood or other tissues.

Biotransformation of EDC has been shown to occur by multiple pathways, in both liver microsomal and cytosol fractions. In the mouse and rat up to 90% of low oral or inhalation doses (<50 mg/kg) are metabolized, with a decreasing percentage of the dose metabolized as the dose approaches and exceeds saturation of metabolic capacity. Metabolism produced 2-chloroacetaldehyde, S-(2-chloroethyl)glutathione (a half sulfur mustard) and other putative reactive metabolites capable of covalent binding to cellular macromolecules, as well as nonreactive glutathione conjugates from "detoxification reactions." The intensity of covalent binding of reaction metabolites to proteins, lipids and DNA, however, is considerably less than that observed with the carcinogenic bromine analog and other known carcinogens.

Exposure to EDC decreases liver levels of reduced glutathione in a dose-dependent manner. Glutathione plays an important role through glutathione conjugation detoxification mechanisms in protecting against binding and cellular toxicity. Covalent binding, hepatotoxicity and mortality of experimental animals are all reduced by administration of sulfhydryl amino acids or glutathione. Conversely, toxicity is enhanced by low liver and tissue concentrations of glutathione. Phenobarbital and other inducers of P-450 metabolism increase the metabolism of EDC, the toxicity and covalent binding. Fasting reduces glutathione tissue content and increases both the metabolism and toxicity of EDC. Ethanol, acutely or chronically administered, may either enhance or inhibit EDC metabolism and toxicity depending on the tissue alcohol concentration.

9.2. ACUTE, SUBCHRONIC AND CHRONIC TOXICITY

9.2.1. Effects in Humans. The preponderance of reports on the toxicity of EDC to humans was published in the foreign literature (primarily German, Russian, and Polish). Many of these reports involved exposure to high levels of compound, involved single cases or small numbers of individuals, were anecdotal in nature and discussed observations that related to the overall toxicity of this chemical in man, and/or provided little detailed correlation between toxic effects and the amount or duration of exposure. Since detailed reviews of the foreign studies were available from NIOSH (1976) and the U.S. EPA (1979), these sources were used in part as a basis for the following discussion of human health effects. Translations were obtained and evaluated independently for all foreign studies that provided dose-response data of relevance to human risk assessment. Reports in which exposures were not primarily to EDC (i.e., most reports of mixed solvent exposures) were not discussed.

9.2.1.1. ACUTE EXPOSURES

9.2.1.1.1. Case Reports and Surveys.

9.2.1.1.1.1. Oral Exposure. Information on the effects of ingested EDC is available solely from clinical case reports and surveys involving accidental and intentional exposures. Many of the cases involved fatalities and described symptoms and signs of poisoning that preceded death. The progression of signs/symptoms and the outcome/findings of cases in which the quantity of EDC ingested leading to death was reported are summarized in Table 9-18. Ingestion of quantities of EDC estimated to range from 8 to 200 mℓ (≈143-3571 mg/kg, assuming 70 kg body weight) were reported as lethal to adult males. Following ingestion there was often a latent period, generally 30 minutes to 3 hours, prior to the onset of symptoms. Symptoms were indicative of CNS effects and gastro-

TABLE 9-18

Effects Associated with Acute Lethal Oral Doses of Ethylene Dichloride in Humans

Patient[a] Sex/Age	Amount Ingested	Symptoms and Signs	Outcome and Findings	Reference
4 males/20 to 29 years	150 to 200 mℓ (≈188 to 250.6 g)	Symptoms were not specified, but appeared after 3 to 4 hours.	Deaths after 10, 15, 33 and 35 hours. Punctuate hemorrhaging in the epicardium, pleura, and mucous membranes of the stomach and duodenum; varying degrees of liver damage with focal hemorrhaging in one case; yellow-white fibrinous bundles of blood in the heart cavities and lesser circulatory vessels; hemolytic jaundice of the endocardium, aortal intima, and dura mater; evidence of decomposition of circulating erythrocytes	Bryzhin, 1945[b]
3 males/19 to 27 years	70, 80 and 100 mℓ (≈87.7, 100.2 and 125.3 g)	Onset of symptoms within a few minutes: vomiting; weakness; dizziness; lost consciousness	Deaths after 5 to 8 hours Hyperemia and hemorrhagic lesions (see text); evidence of overt bleeding into the visceral organs	Kaira, 1966[b]
Male/NS[a]	≈82 mℓ (≈102.7 g) mixed with coffee and beer	Intoxication; vomiting; diarrhea; unconsciousness; dypsnea	Death after 6 hours Hyperemia and hemorrhagic lesions (see text)	Noetzel, 1944[b]
Male/63 years	2 oz. (≈75.2 g) mixed with orange juice and ginger ale	Onset of symptoms after 2 hours: nausea; faintness; vomiting. Subsequently, cyanosis; dilated pupils; coarse rales; weak and rapid pulse; diarrhea; increased cyanosis; absence of pulse and heart sounds; dypsnea	Death after 22 hours attributed to circulatory failure. Extensive hemorrhagic colitis; nephrosis with calcifications of the tubular epithelium and tubular and vascular elastic membranes; fatty degeneration of the liver; spleen and lungs; multiple perivascular hemorrhages of the brain.	Hueper and Smith, 1935

TABLE 9-18

Patient[a] Sex/Age	Amount Ingested	Symptoms and Signs	Outcome and Findings	Reference
Male/16 years	50 mℓ (=62.7 g)	Vomiting; epigastric pain; muscle spasms, hiccups, rapid pulse and lack of eyelid response to light on the 4th day	Death after 91 hours	Roubal, 1947[b]
Male/80 years	50 mℓ (=62.7 g)	Elevated serum enzymes: LDH; SGOT; SGPT; alkaline phosphatase glutamic dehydrogenase; RNAase.	Death within a few hours	Secchi et al., 1968[b]
Male/18 years	50 mℓ (=62.7 g)	Onset of symptoms after 1 hour: somnolence and cyanosis. Diarrhea after 4 hours. Impaired blood coagulation after 5.5 hours: increased prothrombin time; decrease in clotting factors II and V; thrombocytopenia; no increase in fibrinolysis	Death after 17 hours attributed to circulatory shock. Intravascular thrombosis were not found.	Schonborn et al., 1970[b]
Male/57 years	40 mℓ (= 50.1 g)	Somnolence; vomiting; sinus tachycardia; ventricular extrasystoles; regained consciousness after 14 hours; dypnea; loss of blood pressure; cardiac arrest. Impaired blood coagulation observed after 24 hours; prolonged bleeding from venipunctures; reduction in activity of clotting factors II, V, VII and VIII; complete defibrination; thrombocytopenia; increased thrombin time	Death after 24 hours. Thrombi in the pulmonary arterioles and capillaries; hemorrhages into the mucosa of the esophagus, stump of the stomach, rectum and in the subepicardial, subendocardial and myocardial tissues. The coagulation disorder with thrombocytopenia attributed to disseminated intravascular coagulopathy and hyperfibrinolysis	Martin et al., 1969[b]

TABLE 9-18 (cont.)

Patient[a] Sex/Age	Amount Ingested	Symptoms and Signs	Outcome and Findings	Reference
Male/30 years	40 mℓ (≈ 50.1 g)	Slight cough; reddened conjunctivae; shock; weak, rapid pulse. Regained consciousness after 3 hours; hyperactivity alternated with semicomatose condition	Death after 28 hours Hyperemia and hemorrhagic lesions (see text); evidence of overt bleeding into the visceral organs	Garrison and Leadingham, 1954[b]
Male/50 years	≈30 mℓ (≈37.6 g)	Onset of symptoms after 30 minutes: unconsciousness; vomiting; cyanosis; dilated and fixed pupils; pulmonary edema; extreme dypsnea	Death after 10 hours Diffuse hemorrhagic gastritis; bilateral pulmonary congestion; acute necrotizing bronchiolitis and bronchitis; acute toxic nephrosis; diffuse hepatic necrosis; hyperemia of the brain with scattered perivascular hemorrhages in the pons	Lochhead and Close, 1951
Male/55 years (asthmatic)	20 mℓ (≈25.1 g)	Epigastric pain; extreme dizziness; sleeplessness; vomiting; slow pulse	Death after 24 hours	Roubal, 1947[b]
Male/NS	≈20 mℓ (≈25.1 g)	Onset of symptoms after 1 hour: repeated vomiting. Cyanosis and dypsnea after 12 hours	Death after 13 hours	Flowtow, 1952[b]
Male/NS	≈20 mℓ (≈25.1 g)	Symptoms not reported	Death within 12 hours	Flowtow, 1952[b]

TABLE 9-18 (cont.)

Patient[a] Sex/Age	Amount Ingested	Symptoms and Signs	Outcome and Findings	Reference
Male/14 years	15 mℓ (= 18.8 g)	Onset of symptoms after 2 hours: Progressive appearance of severe headache; staggering; lethargy; periodic vomiting; decreased blood pressure; oliguria; dypsnea; somnolence; increased dypsnea; and oliguria, hemorrhagic nasogastric aspirate; ecchymoses; sinus tachycardia; cardiac arrest, pulmonary edema; refractory hypotension. Hypoglycemia on day 2 and hypercalcemia on day 4. Progressive decrease in blood coagulation ability: increased prothrombin time; all clotting factors except VIII were markedly decreased on day 4.	Death after 6 days Extensive mid-zonal liver necrosis; renal tubular necrosis; focal adrenal degeneration and necrosis	Yodaiken and Babcock, 1973
Male/32 years	8 mℓ (≈10 g)	Burning sensation in mouth, throat and stomach; drank milk and vomited; weakness; speech retardation; lethargy; asthenia; cold sweat; muffled heart sound; weak and rapid pulse. 22 hours after ingestion: excitation; restlessness; delirium; flushed face; systolic murmur; respiratory depression; circulatory weakness; anuria	Death after 56 hours	Bogoyavlenski et al., 1968[b]
Male/32 years	glass	Vomiting, weakness, stomach pains. On 3rd day: restlessness, coated and dry tongue; bloody diarrhea; abdomen painful on palpitation; enlarged liver; dry, moist rales; rapid, weak pulse; anuria; increasing cyanosis; unconsciousness	Death on the 3rd day Hyperemia and hemorrhagic lesions (see text)	Agranovich, 1948

TABLE 9-18 (cont.)

Patient[a] Sex/Age	Amount Ingested	Symptoms and Signs	Outcome and Findings	Reference
Male/27 years	half glass	Onset of symptoms after 2.5 hours: Unconsciousness that was regained after 12 hours; vomiting (dark vomitus); burning sensation in the digestive tract; dypsnea; nausea; cyanosis; depressed respiratory rate; moist rales; muffled heart sounds; rapid pulse; extrasystoles; anuria	Death after 19 hours Hyperemia and hemorrhagic lesions (see text); evidence of overt bleeding into the visceral organs	Bogoyavlenski et al., 1968
Male/43 years (alcoholic)	4 drinks diluted with orange juice[c]	Unconsciousness	Death after 8 hours Hyperemia and hemorrhagic lesions (see text); evidence of overt bleeding into the visceral organs and lungs. Death after 24 hours. Hyperemia and hemorrhagic lesions (see text); evidence of overt bleeding into the visceral organs and lungs	Hulst et al., 1946[b]
Male/43 years (alcoholic)	4 drinks diluted with orange juice[c]	Confusion; deep sleepiness; unconsciousness; vomiting with blood	Death after 24 hours Hyperemia and hemorrhagic lesions (see text); evidence of overt bleeding into the visceral organs and lungs	Hulst et al., 1946[b]
Male/NS	several mouthfuls	Onset of symptoms after 30 min: vertigo; nausea; vomiting; slightly muffled heart sound; tachycardia. After 17.5 hours: headache; substernal pain; cyanosis; rapid, weak pulse; dry rales; decreased blood pressure; vomiting with bile; diarrhea; subconjunctival hemorrhage; oliguria; paranephric hemorrhage. 5th day pulmonary edema and unconsciousness	Death on the 5th day	Morozov, 1958[b]

TABLE 9-18 (cont.)

Patient[a] Sex/Age	Amount Ingested	Symptoms and Signs	Outcome and Findings	Reference
Male/63 years	1 or 2 sips	Unconsciousness shortly after ingestion, but soon regained; strong vomiting; period of improvement; unconsciousness again after 10.5 hours; falling blood pressure	Death after 14 hours attributed to circulatory failure. Hyperemia and hemorrhagic lesions (see text)	Freundt et al., 1963[b]
Male/1 1/2 years	1 sip	Extreme weakness; comatose; vomiting	Death the next day Hyperemia and hemorrhagic lesions (see text)	Keyzer, 1944[b]
Male/79 years	1 sip	Vomiting; weakness; pale; cyanosis; scarcely conscious; vagueness; rapid, regular pulse; blood pressure not measurable	Death after 40 hours attributed to heart and circulatory failure. Hyperemic and hemorrhagic lesions (see text)	Weiss, 1957[b]
Male/2 years	1 sip	Vomiting; diarrhea; tonic spasms; increasing loss of consciousness; dypsnea; impaired circulation	Death after 20 hours Hyperemia and hemorrhagic lesions (see text)	Reinfried, 1958[b]
Male/23 years	1 sip	Onset of symptoms after 1 hour: dizziness; nausea; unconsciousness; vomiting; cyanosis; no pupil reaction; no corneal reflex; dypsnea; strong motor unrest.	Death after 8 hours attributed to respiratory and circulatory failure Hyperemia and hemorrhagic lesions (see text); evidence of overt bleeding into the visceral organs	Reinfried, 1958[b]

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[a] NS = Not stated

[b] Data compiled from NIOSH, 1976

[c] Presumably EDC was mixed instead of alcohol

intestinal disturbances, and frequently included dizziness, nausea, headache, periodic vomiting, diarrhea, epigastric pain or tenderness, dilated pupils and lack of corneal reflex, rapid and weak pulse rates, progressive cyanosis, dyspnea and unconsciousness. These symptoms of toxicity are characteristic of those produced by many of the chlorinated aliphatic hydrocarbons. Somnolence, oliguria and anuria, muffled heart sounds and motor unrest have also been described in a number of cases.

The results of several health surveys of large numbers of orally exposed individuals have recently been reported by Russian investigators, and summarized by U.S. EPA (1979) (Akimov et al., 1976, 1978; Shchepotin and Bondarenko, 1978; Bonitenko et al., 1974, 1977; Luzhnikov et al., 1974; Luzhnikov and Savina, 1976) and Chemical Abstracts (Andriukin, 1979). Information regarding the design of these surveys is not available, and dosage information is either not available or not adequately reported (i.e., not correlated with effects) (Table 9-19). The clinical symptoms and signs of exposure recorded in the surveys are consistent with those described in single case reports (see Table 9-18) (i.e., neurological effects and evidence of liver and kidney dysfunction), but there appears to be a more frequent indication of cardiovascular insufficiency. The range of doses that elicited effects in the surveys (≃12.5 to 250.6 g) also appear to be consistent with the single case reports (see Table 9-18), but incidences of fatalities were not presented in the available summaries. Although none of the effects reported in the surveys were correlated with specific doses, several of the studies indicated that the severity of poisoning was related to blood levels of EDC (Bonitenko, 1974, 1977; Luzhnikov et al., 1974, 1976).

The clinical syndrome of oral EDC poisoning in children is similar to that seen in adults, but the lethal dose range is somewhat lower (0.3 to 0.9 g/kg) (Hinkel, 1965). This range of doses did not always cause death, and is derived

TABLE 9-19

Effects of Acute Oral Ingestion of 1,2-Dichloroethane (Survey Results)

Route	No. of Subjects	Dose	Principal Findings	Reference
Oral	121	20 to 200 mℓ (≈25 to 250.6 g)	Mild to severe poisoning characterized by pronounced DCE odor on breath (91%), dry skin (75%), hypotension (74%), extreme pupil dilation (72%), mucosal cyanosis (67%), tachycardia (62%), respiratory difficulty (59%), muscular hypotonia (46%), decrease in tendon reflexes (46%), loss of consciousness (42%). Neurological syndromes noted in 118 subjects: comatose (42%), atactic (42%), asthenic with autonomic vascular insufficiency (27%), extrapyramidal (23%), convulsive (7.4%), psychotic (5%). Lethality not reported.	Akimov et al., 1976, 1978
Oral Inhalation	211 37	NR NR x 20 to 30 minutes	Aggregate findings for 248 total patients reported. Neurological disorders (incl. unconsciousness, respiratory depression) (100%), cardiovascular insufficiency (incl., arrhythmias, hypotension, reduced cardiac output, decreased peripheral resistance) (60%), liver dysfunction (incl., enlargement, hyperbilirubinemia, increased serum albumin and asparagine transaminase (35%). Nephropathology (oliguria, proteinuria, azotemia, acute renal failure with disturbed acid/base balance) particularly associated with inhalation exposures. Gastroenteritis milder in subjects exposed via inhalation. No correlation between severity of poisoning and the blood or urine concentration or the amount inhaled.	Schepotin and Bondarenko, 1978
NR^a	110	NR	Acute gastritis with vomiting (77%), neurological disorders including coma (81%), acute cardiovascular insufficiency (57%), hepatitis (56%) with liver enlargement and dysfunction (abnormal bromosulfalein, plasma bilirubin, plasma glutamine - aparagine transaminase). Clinical symptoms of poisoning were observed at blood concentrations of 0.5 mg %, and coma developed at 5 to 7 mg %.	Lushnikov et al., 1976, 1978

TABLE 9-19 (cont.)

Route	No. of Subjects	Dose	Principal Findings	Reference
NS[a]	160[b]	NA	Hemodynamic shock due to myocardial dysfunction. Characterized by compensatory (increased peripheral resistance, normal or slightly increased arterial blood pressure, decreased cardiac output and blood volume, decreased cardiac isometric contraction, increased ventricular expulsion time, asynchronous contractions) and decompensatory (pronounced and progressive hypotension, decreased cardiac output, normal or slightly decreased peripheral resistance, decreased myocardial contractile force during ventricular systole, prolonged periods of asynchronous contractions) phases. EKG changes including arrhythmias observed in both compensated and decompensated shock. Pathologic changes in the myocardium characterized by capillary endothelial cell edema, capillary lumen stenosis, edema of the myocardial interstices with leukocyte accumulation and microfocal hemorrhages, decreased glycogen, degenerative changes, and decreased mitochondrial enzyme activities.	Luzhnikov et al., 1976, 1978
Oral Inhalation	24 3	10 to 100 mL (≈12.5 to 125 g) NR	17 patients exhibited manifestations of light/mild poisoning: headache, vertigo, abdominal pain, nausea, vomiting, and signs of cardiac insufficiency (increased contraction rate, decreased minute volume, decreased circulating blood volume, decreased cardiac index); 5 of 17 had hepatomegaly, icteric skin, sclera, and increased bilirubin levels. The other 10 patients were comatose and had more pronounced symptoms of cardiac insufficiency.	Andriukin, 1979
Oral	32	NR	Gastroenteritis and proteinuria. Elevated leukocyte count and elevated alanine/aspartate aminotransferase activities correlated with severity of poisoning. Coma was associated with blood concentrations of 15 to 30 mg %, and consciousness returned at levels below 8 to 10 mg %. Adipose tissue and blood levels of 68 and 1.2 mg %, respectively, at autopsy.	Bonitenko et al., 1974, 1977

TABLE 9-19 (cont.)

Route	No. of Subjects	Dose	Principal Findings	Reference
Oral[c]	7 children (1 to 6 years)	NR	Clinical syndrome similar to that in adults: severe and persistent vomiting (within 1 hour), and subsequent (immediate to 10 to 12 hours) narcotic effects (e.g., somnolence, motor unrest, reflex increases, convulsions or coma). Less frequent indications of circulatory failure, kidney and liver functional disturbances, and tachycardia. No remarkable hematologic changes. Typical pathological anatomical findings. LD_{20} reportedly ranged from 0.3 to 0.9 g/kg.	Hinkel, 1965

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[a] Route is probably oral, but not specifically stated in the EPA (1979) summary of this study.

[b] The EPA summary of this study stated that "at least" 160 patients were studied.

[c] Exposure to a "nerve balsam" medicine that was 75% 1,2-dichlorethane (other components not stated in EPA summary).

from a review of seven cases of accidental poisoning in children that ranged in age from 1 to 6 years.

Foreign reports of individual non-fatal cases of EDC ingestion (Ienistea and Mezincesco, 1943; Bloch, 1946; Stuhlert, 1949; Flowtow, 1952; Kaira, 1966; Rohmann et al., 1969; Gikalov et al., 1969; Pavlova et al., 1965; Agranovich, 1948) were in most instances not detailed in the NIOSH (1976) or U.S. EPA (1979) reviews, presumably because the effects were similar to those that preceded death with lethal exposures, and because the quantities ingested were not known. Bloch (1946) did note bloody diarrhea and evidence of adverse liver (enlargement, slightly increased serum bilirubin, urobilinogen, abnormal galactose and alcohol load test results) and kidney (oliguria, albumin and casts in the urine, temporary retention of nitrogenous substances) effects in one man who claimed to have swallowed "only a small amount" of EDC.

Death was usually ascribed to circulatory and respiratory failure, and autopsies revealed tissue congestion, cellular degeneration, necrosis and hemorrhagic lesions of most organs, including the stomach, intestines, liver, kidneys, spleen, heart, lungs, respiratory tract and brain (see Table 9-18). There was occasionally evidence of gross bleeding into the visceral organs or lungs. Several of the more recent reports (Martin et al., 1969; Schonborn et al., 1970; Yodaiken and Babcock, 1973) indicated that the hemorrhagic effects may have been exacerbated by a condition known as disseminated intravascular coagulation (DIC). DIC is characterized by a depletion (consumption) of clotting factors, hypofibrinogenemia and thrombocytopenia, and the resultant effect is a severe bleeding tendency.

The results of the studies by Luzhnikov and coworkers (1976, 1978) suggest that EDC can exert a direct toxic effect on the myocardium (see Table 9-19). Pathologic examinations of EDC exposed individuals (amount ingested and number examined not available) revealed significant edema in the capillary endothelial cells and stenosis of the capillary lumens, pronounced edema of the myocardial interstices with accumulation of polymorphonuclear leukocytes, microfocal hemorrhages, diminished glycogen content, and degenerative changes. Mitochondrial damage was indicated by a decrease in enzyme activities. Myocardial functional changes (e.g., decreased contractile force, asynchronous contractions) were also observed prior to death. The cardiotoxic effect of EDC apparently precipitated a clinical state of shock; hemodynamic disorders commonly observed in at least 160 patients included increased peripheral resistance, decreased cardiac output, hypotension and EKG changes including arrhythmias.

9.2.1.1.1.2. Inhalation Exposure. Reports of numerous cases of acute occupational exposure to EDC vapor have been published (NIOSH, 1976). These acute exposures have involved both fatal (27 cases) (Wendel, 1948; Brass, 1949; Hadengue and Martin, 1953; Ollivier et al., 1954; Domenici, 1955; Salvini and Mazzuchelli, 1958; Guarino and Lioia, 1958; Troisi and Cavallazzi, 1961) and nonfatal (57 cases) outcomes (Wirtschafter and Schwartz, 1939; Jordi, 1944; Agronovich, 1948; Baader, 1950; Paparopoli and Cali, 1956; Menschick, 1957; Smirnova and Granik, 1970), but none of the reports provided exposure concentrations. Furthermore, although EDC was usually reported to be the primary vapor to which the workers were exposed, the preponderance of exposures were to poorly characterized mixtures of EDC and other solvents, or to EDC of unknown purity. The occupational exposures were generally associated with maintenance and cleaning operations or the use of EDC as a paint thinner, but many (39 cases) involved exposure to Granosan, a fumigant composed of 30% carbon tetrachloride and 70% EDC (Domenici, 1955; Salvini and Mazzucchelli, 1958; Guarino and Lioia, 1958; Paparopoli and Cali, 1956).

The effects associated with the above cited fatal and non-fatal acute inhalation exposures were very similar to those found after ingestion (NIOSH, 1976). In general, the initial symptoms appeared to be consistent with both CNS effects (headache, dizziness, lethargy, feelings of drunkenness, unconsciousness) and gastrointestional disturbances (nausea, vomiting, diarrhea), which are characteristic of chlorinated aliphatic hydrocarbon toxicity. In some cases workers were asymptomatic and were not overcome during exposure, but later became unconscious. Other signs and symptoms of inhalation exposure commonly included cyanosis, epigastric tenderness and/or pain, hepatomegaly, and jaundice.. Laboratory studies were consistent with these observations and indicative of hepatic dysfunction (increased serum bilirubin and urobilinogen, hypoglycemia, abnormal function tests) and renal disturbances (oliguria, anuria, abnormal function tests). In addition, conjunctivitis, respiratory tract irritation and inflammation, rales and leukocytosis were occasionally associated with the acute vapor exposures.

Death from acute inhalation exposure was generally attributed to respiratory and circulatory failure (NIOSH, 1976), although it is not certain if EDC exerted a direct toxic effect on the cardiopulmonary system or precipitated a shock-like state which could have elicited many of the changes observed at autopsy. Autopsies frequently revealed pulmonary edema, congestion of internal organs (liver, kidneys, spleen, lungs, brain) and cellular degeneration and necrosis (liver and kidneys). Hyperemia and hemorrhagic lesions were also observed in the kidneys, brain, respiratory tract, lungs, and heart.

9.2.1.1.1.3. Dermal Exposure. Several reports described instances (a total of 6 cases) in which skin contact with EDC occurred concurrently with inhalation exposures (Wirtschafter and Schwartz, 1939; Anonymous, 1946; Rosenbaum, 1947; Hadengue and Martin, 1953). Severe dermatitis was a commonly reported result of the dermal exposures, as is the case with many chlorinated hydrocarbons which produce defatting of the skin. Several of these reports also suggest that dermal absorption may significantly contribute to total exposure (characteristic symptoms of intoxication were noted in workers who were wearing EDC-soaked clothing).

9.2.1.1.2. Experimental Investigations.

9.2.1.1.2.1. Physiologic Effects. Borisova (1957) examined eye sensitivity to light and plethysmographic and spirographic responses in a small number of subjects (3 to 4) who were experimentally exposed to concentrations of EDC that ranged from ≃1 to 12.4 ppm (4 to 50 mg/m^3). This range of concentrations represented subthreshold, threshold and above threshold odor perception concentrations (Section 7.1.2.2). The concentration of EDC in air was determined nephelometrically; the method is sensitive enough (0.001 mg/sample reported) to monitor EDC at levels lower than the lowest concentration tested (4 mg/m^3).

In the light sensitivity experiment baseline perception thresholds were determined prior to the exposures for each of 3 subjects (17 to 24 years old), and the subjects inhaled EDC vapor for 15 minutes prior to testing (Borisova, 1957). When tested after 40 minutes of dark adaptation, the threshold (intensity) at which light was perceived was found to be higher during exposure to EDC, and the threshold appeared to increase with increasing concentrations of EDC (Table 9-20). No change in the light sensitivity of eyes was observed in any of the subjects at 1 ppm, and the lowering of eye sensitivity to light was most marked at 12.4 ppm.

The effect of low concentrations of EDC on blood volume (vascular constriction) and pulse fluctuations was studied with a finger plethysmograph (Borisova, 1957). Four subjects were exposed to vapor concentrations of 1, 1.5, 3, 5.7 and 12.4 ppm for 30 seconds or 15 minutes. A 30 second exposure at

TABLE 9-20

Effect of Ethylene Dichloride Exposure on Eye Sensitivity to Light[a]

Concentration ppm (mg/m^3)	Perception Threshold[a] (Units of Optical Density)		
	Subject 1	Subject 2	Subject 3
1 (4)	no effect	no effect	no effect
1.5 (6)	-0.2	<0.05	no effect
2.2 (9)	-0.25	-0.3	+0.15
3 (12)	-0.25	-0.25	no effect
4.3 (17.5)	-0.3	-0.35	-0.45
5.7 (23.2)	-0.45	-0.4	-0.25
6.2 (25)	-0.45	-0.5	-0.7
7.4 (30)	-0.5	-0.5	-0.75
12.4 (50)	-1.2	-1.2	-0.6

Source: Borisova, 1957

[a] Eye sensitivity to light was determined after 40 minutes of adaptation in the dark at different EDC concentrations.

1.5 ppm resulted in a temporary vasoconstriction in all 4 subjects. Complete data was not reported, but vasoconstriction appeared to be more pronounced at 3 ppm and higher concentrations. Results of tests in which EDC exposure was extended to 15 minutes reportedly showed that the above concentrations caused "characteristic changes" in the plethysmograms of all subjects that included increased pulse beat, pulse waves, and pulse amplitude. The observations at the higher concentrations in both the 30-second and 15-minute exposure experiments also suggested that the degree of response was proportional to the exposure concentration. Exposure to concentrations of 1.5, 3, 5.7, and 12.4 ppm for 1 minute produced changes in depth of breathing in 4 subjects (as indicated by increased amplitude of respiratory waves on spirograms), but concentrations of 1 ppm reportedly had no effect on respiration (Borisova, 1957).

9.2.1.1.2.2. Odor Detection and Recognition Thresholds. Hellman and Small (1973, 1974) determined an absolute odor threshold of 6.0 ppm and an odor recognition threshold of 40 ppm for EDC. A trained odor panel was used to characterize the odor properties of this compound and 101 other petrochemicals, but the number of panelists was not stated. The absolute odor threshold is the concentration at which 50% of the odor panel observed an odor, and the recognition threshold is the concentration at which 100% of the panel defined the odor as representative of EDC. Borisova (1957) determined the odor threshold of EDC with 20 subjects and a total of 1256 tests. Thirteen subjects perceived EDC vapor at a concentration of approximately 6 ppm (23.2 to 24.9 mg/m^3), 6 subjects perceived EDC at 4.5 ppm (17.5 mg/m^3), and 1 subject detected the compound at 3 ppm (12.2 mg/m^3).

When diluted in water, the odor recognition threshold of EDC was determined to be 29 ppm (v/v water) (Amoore and Venstrom, 1966). An odor panel of 13 men and 16 women was used for the determination, and the threshold defined by the panelists was the concentration of EDC that yielded 70% correct response (significant at the 1% level) in a paired comparison against pure water as a control.

9.2.1.2. REPEATED AND CHRONIC EXPOSURES.

9.2.1.2.1. Case Reports -- Repeated exposure to EDC vapor in the workplace has resulted in effects which are consistent with those resulting from acute exposures. Symptoms and signs including anorexia, nausea, vomiting, weakness and fatigue, nervousness, epigastric pain/discomfort and irritation of the respiratory tract and eyes were described in numerous case reports of industrial exposures (McNally and Fostvedt, 1941; Siegel, 1947; Rosenbaum, 1939; Watrous, 1947; Rejsek and Rejskova, 1947; Delplace et al., 1962; Suveev and Babichenko, 1969). In one study (Suveev and Babichenko, 1969), examination of 12 symptomatic workers that were brought to a clinic revealed paleness and cold sweat (12 of 12), bradycardia (9 of 12), systolic murmur (5 of 12), diarrhea (5 of 12; 3 of 12 with blood) and enlarged livers that were soft and tender to palpitation (9 of 12); muffled heart sounds, increased rate of respiration, rales, coated and dry tongues were also observed but incidences of occurrence were not stated. Signs indicative of nervous system dysfunction have also been reported in cases of chronically exposed workers; these include nystagmus, fine tongue tremors and sluggish patellar reflex (McNally and Fostvedt, 1941), encephalic disorders (Delplace et al., 1962), and decreased muscle tone, loss of reflexes, a positive Romberg's sign, and deafness (Suveev and Babichenko, 1969). Complaints of hand and arm eczema that appeared within the first year of exposure were recorded in 11 of 16 cases by Delplace et al. (1962). It should be noted that exposure concentrations and information on the types of exposures were not provided in any of the above cited reports.

Rosenbaum (1947) discussed experiences with cases of EDC intoxication in Russian industries from 1934 to 1945. He observed over a period of 10 years that characteristic symptoms of acute poisoning could develop with repeated exposure to concentrations of 75 to 125 ppm in air. Fatalities have resulted when workers experienced these symptoms 2 or more times in a period of 2 to 3 weeks. There was no mention, however, of the number of people affected or durations of exposure.

Byers (1943) noted that a "number of persons" exposed to EDC complained of delayed toxic effects. The workers stated that the worst effects, which varied from lassitude and malaise to nausea, vomiting and abdominal pain, occurred after the evening meal. These symptoms were associated with exposure to concentrations "only slightly in excess of 100 ppm for 7.5 hours daily", and were not completely alleviated when ventilation procedures reduced the EDC concentration to 70 ppm.

Exposure conditions were described in partial detail for 2 workers who were chronically exposed to EDC for 7 and 9 months during the manufacture of hexachlorophene (Guerdjikoff, 1955). EDC was used as a catalyst in this process. During one of the operations, which was repeated for 2 to 3 minutes several times a day for a total of about 30 minutes, exposures were associated with adding EDC, trichlorophenol and sulfuric acid to the reaction vat. EDC exposure concentrations were not measured during the filling operations, but the workers wore an air-supplied respirator and were probably only exposed to EDC occasionally due to improper fit. During another operation which lasted 10 minutes and was repeated 3 to 4 times a day, the exposure concentration of EDC was about 120 ppm. During a final operation, the workers were exposed once a day for ≈10 to 15 minutes when an EDC pipe was cleaned; these exposure concentrations were not measured but were considered by Guerdjikoff (1955) to be more than 120 ppm. Both workers exhibited similar symptoms, typical of EDC exposures, of anorexia, epigastric pain, fatigue, irritability, and nervousness after about 3 weeks of exposure. Neurological effects such as hand tremors, hyperhidrosis, and difficulty in walking were eventually experienced.

9.2.1.2.2. Health Surveys -- Kozik (1957) reported the results of a health and morbidity survey of Russian aircraft industry workers. All of the workers in the study group (size not stated) were employed in a shop where glue that contained EDC as a solvent was used to bond rubber sheets to metal forms in a soft tank fabrication process. Most of these workers were gluers, but a small number worked inside the completed tanks to disassemble the forms. EDC was emitted to the air during application and glue drying.

About 500 atmospheric measurements of EDC were reported to have been taken (Kozik, 1957). Although the sampling and analytical methods were not mentioned, NIOSH (1976) felt that the data were presented in sufficient detail to permit estimations of TWA exposures. NIOSH estimated that 44 to 46% of the total exposure occurred during the gluing operations, when the TWA concentrations were ≈28 ppm during application and ≈16 ppm when the glue was drying. When other operations were performed in the same shop (during the second half of the work-shift), the EDC TWA concentrations were ≈11 ppm. The TWA for the total shift was estimated to be 15 ppm. Concentrations ranged from approximately 4 to 50 ppm; concentrations in excess of 20 ppm were associated only with the gluing and drying operations and occurred about 15% of the time. NIOSH (1976) has noted, however, that the aforementioned TWA concentrations may be an overestimate of most of the workers' exposures for several reasons. First, the tabulation of measurements in the glue application category also contained high values (45 to 52 ppm) that were experienced only by an insignificant number of workers who disassembled the molds within the finished tanks. Second, the measurements were apparently not breathing zone measurements and third, the ventilation system was designed with the exhaust ducts on the floor. In light of these considerations, NIOSH concluded that a more realistic appraisal of the TWA exposure of the majority of the workers is 10 to 15 ppm.

Workers (total number not stated) who were engaged in the production of soft tanks during the years 1951 to 1955 experienced increased morbidity and lost workdays when compared with workers in the entire factory (Table 9-21). Disease categories examined included acute gastrointestinal disorders, neuritis and radiculitis, and other diseases. An in-depth analysis of the morbidity rate with temporary disability for 1954 to 1955 reportedly showed high rates for gastrointestinal diseases, liver and gall bladder diseases, and diseases of the muscle, tendons and ganglion (Table 9-21). The liver and gall bladder diseases were considered by Kozik (1957) to be related to a specific toxic effect of EDC (the dyspeptic symptoms it causes reportedly are often diagnosed as gastritis), but the diseases of the muscle, tendon and ganglia were associated with the numerous repetitive motions the workers had to make when applying the glue. Further examination of 83 of the gluers revealed diseases of the liver and bile ducts (19 of 83), neurotic conditions (13 of 83), autonomic dystonia (11 of 83), asthenic conditions (5 of 83), and goiter and hyperthyroidism (10 of 83).

Visual-motor reactions were studied at the beginning and end of 14 workdays in 17 of the gluers and 10 control machinists (Kozik, 1957). It was stated that a device was used to determine simple and complex reaction (color differentiation) times, as well as reaction times in a modification of the complex reaction task; a total of 3700 reaction tests were conducted, but details of the tests were not given. A comparison of the mean rates for all three reactions show no significant differences in the two groups either before or after work. Nervous system dysfunction was suggested, however, by the inadequately reported results of the complicated reaction tests. "Most" of the gluers made errors in the complex reaction task, while the machinists did not make any errors (additional data are not available). In the modified complex reaction test, errors were committed

TABLE 9-21

Morbidity and Lost Workdays of Aircraft Industry Gluers Exposed to Ethylene Dichloride[a]

(Rates/100 Workers)

Year		Total Morbidity		Acute Gastro-intestinal Disorders		Neuritis and Radiculitis		Other Diseases		Liver and Gall Bladder Diseases[b]	Acute Gastritis[b]	Chronic Gastritis[b]	Diseases of the Muscles, Tendons, and Ganglia[b]
		Plant	Shop	Plant	Shop	Plant	Shop	Plant	Shop				
1951	Cases	120.2	159.8	5.1	11.6	5.2	13.0	34.4	43.2	-	-	-	-
	Days	995.8	1445.5	19.3	43.5	59.9	127.0	354.2	541.8	-	-	-	-
1952	Cases	124.0	137.6	4.2	5.7	5.0	9.7	34.0	40.8	-	-	-	-
	Days	960.9	996.0	15.1	23.1	44.8	94.5	335.2	378.7	-	-	-	-
1953	Cases	135.6	163.9	14.4	6.2	7.5	16.5	35.3	53.5	-	-	-	-
	Days	1040.8	1236.5	15.6	19.1	67.3	146.0	338.3	524.0	-	-	-	-
1954	Cases	150.7	191.8	5.3	9.6	7.9	16.7	40.8	63.8	21	13	6	48
	Days	1175.9	1563.2	19.3	31.8	73.8	182.8	386.4	596.2	251.5	64.5	45	170
1955	Cases	127.6	176.6	3.6	5.0	5.9	10.3	37.9	63.3	24	8	3	8
	Days	978.4	1462.4	12.1	15.3	51.1	90.2	345.7	640.5	290	27	14	50

[a] Source: Kosik, 1957

[b] The incidences are reportedly elevated, but reference values were not given.

both before and after work by 15 of 17 gluers; 4 of 10 machinists made errors, but only at the end of the workday.

Cetnarowicz (1959) investigated the possibility of EDC poisoning in Polish oil refinery workers. The workers were employed in a mineral oil purification (dewaxing) process that involved mixing oils with a solvent that contained 80% EDC and 20% benzene at 40°C; the mixture was subsequently cooled to -24°C, and precipitated paraffin was separated by centrifugation. Durations of exposure were not stated, but concentrations of EDC ranged from ≈10 to 200 ppm (0.04 to 0.8 mg/ℓ), with the highest excursions in the centrifuge room (Table 9-22). Benzene concentrations ranged from ≈3.1 to 7.8 ppm (0.01 to 0.025 mg/ℓ), but were not specifically reported for the different work areas detailed in Table 9-22. Nineteen workers (18 to 48 years old; 18 men, 1 woman) that had been employed for 2 to 8 months were included in the initial study group; 2 men and the woman were not examined due to medical history complications. The results of these examinations are summarized in Table 9-23 and in the text below.

Ten of the 16 workers were employed in the centrifuge room, where EDC concentrations ranged from 62 to 200 ppm. All 10 of these workers complained of a burning sensation in the eyes and lacrimation, and 6 of the 10 workers stated that they had experienced dryness of the mouth, an unpleasant sweet aftertaste, dizziness, fatigue, drowsiness, nausea, occasional vomiting, constipation, and loss of appetite. Three of these workers also complained of pain in the epigastrum. All of the above-mentioned subjective complaints disappeared when the workers changed workplaces, but reappeared upon reexposure. Of the 6 workers employed in the pump and recrystallization rooms (10 to 37 ppm), only 1 complained of similar symptoms. As detailed in Table 9-23, clinical evaluation of the 16 workers indicated the likelihood of liver effects (tenderness to palpitation with minimal enlargement, epigastric pain, elevated urobilinogen

TABLE 9-22

Concentrations of Ethylene Dichloride in Oil Refinery Mineral Oil Purification Process Air*

Location	ppm (repeated measurements)		
Centrifuge room	64	62	200
Pump room 1	16	10	17
Pump room 2	25	13	-
Pump room 2	30	37	-
Crystallization room	30	37	-

Source: Derived from Cetnarowicz, 1959 by NIOSH, 1976.

TABLE 9-23

Effects Observed in Polish Oil Refinery Workers*

Concentration of 1,2-DCE[a]	Effect	Incidence
62, 64 and 200 ppm	Dryness of the mouth; unpleasant sweet aftertaste; dizziness; lassitude; sleepiness; nausea; vomiting; poor appetite	6/10[b]
	Burning sensation of the eyes that disappeared with adaptation to the atmosphere	10/10[b]
	Epigastrium pain	3/10[b]
	Insignificant tenderness of the epigastrium	7/10[b]
	Livers tender to palpitation with minimal enlargement	4/10[b]
	Normal arterial blood pressure	10/10[b]
	Relaxed pulse (60 to 65/minutes)	6/10[b]
	Intensified reflexes and automic neuroses	3/10[b]
10 to 37 ppm	Complaints similar to those associated with exposure to 62, 64 and 200 ppm	1/6[c]
10 to 200 ppm	Sweet aftertaste; dizziness; nausea; vomiting; lack of appetite	6/42[d]
	Livers tender to palpitation with insignificant enlargement	3/42[d]
	Epigastrium pain	2/42[d]
	Emaciation (2 to 10 kg below expected weight)	16/16
	Unremarkable opthalmologic examination	16/16
	Unremarkable examination of upper respiratory tract, lungs, and heart	16/16
	Augmented reflexes and vegetative neurosis	3/16

TABLE 9-23 (cont.)

Concentration of 1,2-DCE[a]	Effect	Incidence
10 to 200 ppm (cont.)	Icteric skin coloration	1/16
	Elevated urobilinogen levels	"majority" of 16
	X-ray observable chronic catarrh of the stomach with atrophy of the mucous membrane	6/16
	Periodic spasm of the pylorus	3/16
	Moderate hyperchromic anemia (3,430,000 erythrocytes/cu mm and 60% hemoglogin)	1/13[e]
	Slight reticulocytosis (0.1 to 0.3%)	4/13[e]
	Diminished osmotic fragility of erythrocytes in NaCl	6/13[e]
	Slight leukocytes (11,200/cu mm)	1/13[e]
	Low platelet count (40,000 to 55,000 cu mm)	2/13[e]
	Decreased number of neutrophils (40 to 50%)	2/13[e]
	Slightly increased number of neutrophils (70 to 78%) with decreased number of lymphocytes (15 to 25%)	6/13[e]
	"Abnormal" distribution of white blood cells	4/13[e]
	Increased number of erythrocytes, increased percentage of polymorphonuclear neutrophils, mild stimulation of erythropoiesis with a less significant increase of leukopoiesis in the bone marrow	5/13[e]
	Elevated serum bilirubin (2.3 mg %)	1/16

TABLE 9-23 (cont.)

Concentration of 1,2-DCE[a]	Effect	Incidence
10 to 200 ppm (cont.)	Elevated blood nonprotein nitrogen (55 mg %)	1/16
	Normal overall quantity of serum protein	16/16
	Diminished serum albumin	6/16
	Elevated serum globulin levels	8/16
	Diminished blood fibrin content	3/16
	Positive Takata-Ara liver function test	4/16
	Borderline Takata-Ara liver function test	5/16
	Positive Cadmium turbidity test	6/16
	Borderline Cadmium turbidity test	5/16
	Negative glucose tolerance test	8/16
	Decreased secretion of gastric hydrochloric acid	12/16
	X-ray observable catarrhal changes of gastric mucosa	6/16
	Periodic pyloric spasms	3/6[f]

Source: Cetnarowicz, 1959 (derived from NIOSH, 1976)

[a] Concurrent exposure to ≈3 to 8% benzene (see text)

[b] Workers employed in the centrifuge room (see Table 9-22)

[c] Workers employed in the pump and crystallization rooms (see Table 9-22)

[d] 42 workers initially examined; effects on these workers prompted further examinations of 16 workers from one shift (see below).

[e] Hematological examinations were performed on 13 workers.

[f] 3 of the 6 with catarrh

levels, positive Takata-Ara liver function tests, negative glucose tolerance tests), and changes in the gastrointestinal tract (X-ray observable chronic gastritis with mucosal inflammation, pyloric spasms, impaired hydrochloric acid secretion). The distribution of these findings by room (i.e., high or low exposure) was not, however, given. Other abnormal findings included blood and bone marrow changes that may be attributable to the concurrent exposure to benzene (Table 9-23).

Rozenbaum (1947) reported the results of studies of approximately 100 Russian workers from different industries (not specified) who had experienced exposure to EDC at levels below 25 ppm ($\leq$0.1 mg/ℓ) in air for 6 months to 5 years. "Many" of these workers exhibited non-specific functional nervous system disorders (e.g., red dermographism, muscular torus, bradycardia, increased perspiration), and "some" of the subjects complained of fatigue, irritability, headaches and insomnia. Hematologic or functional organ changes (not elaborated) were not, however, noted. The incidence of the observed effects, average exposure concentrations, the range of exposure concentrations to which the workers were exposed and information on experimental design were not reported.

Brzozowski et al. (1954) considered that absorption of EDC through the skin was largely responsible for adverse health effects among certain agricultural workers in Poland. EDC was used as a fumigant and work practices involved transport of the liquid to fields in barrels, pouring the EDC by hand into buckets, carrying the open buckets to the site of application, and pouring the EDC into a series of holes in the ground. The workers were exposed to particularly high concentrations of EDC vapor during pouring. Significant dermal exposure is indicted by the frequent spilling of quantities of EDC on clothes and sleeves during the transport of the open buckets to the places of application (resulting in soaked clothing that was not changed), and by the fact that the workers used EDC to wash their skin. A single atmospheric sample, comprising 10 subsamples collected from locations representative of the working zone (the collection apparatus was moved from place to place with the workers), showed a concentration of 4 ppm of EDC. Because of the practical difficulties of sample collection (the workers did not stay at one location sufficiently long to collect an entire sample), conditions were simulated in a laboratory to better estimate potential exposure concentrations. Analysis of laboratory samples showed concentration of ≈14.5 to 15 ppm; a sample taken during the pouring of EDC into buckets, considered to be the maximum exposure of a worker, contained 60 ppm.

Medical examinations were performed on 118 of the agricultural workers (Brzozowski et al., 1954). Ninety had positive findings that included conjunctival congestion (82/118), weakness (54/118), reddening of the pharynx (50/118), bronchial symptoms (43/118), metallic taste in the mouth (40/118), headache (39/118), dermatographism (37/118), nausea (31/118), cough (30/118), liver pain (29/118), conjunctival burning sensation (24/118), tachycardia (21/118), and dyspnea after effort (21/118). The Quick Test for hippuric acid was used to evaluate liver function and was reported to be positive in 40 of 56 investigations. Skin sensitization tests with pieces of gauze soaked with 0.1% EDC in alcohol or 50% EDC in soybean oil were reportedly negative when scored after 40 hours of contact, but the number of workers tested was not stated.

9.2.2. Effects in Animals

9.2.2.1. ACUTE EXPOSURE

9.2.2.1.1. Exposure -- The observed toxic effects of ingested EDC in laborabory animals summarized in Table 9-24 tend to confirm the findings from cases involving human oral exposures. The LD_{50} for a single oral exposure was reported to be 680 mg/kg in a study that employed 80 rats and 4 dosage levels (McCollister et al., 1956) and 770 mg/kg in a range-finding study of rats (Smyth et al., 1969). These data suggest that EDC is moderately hazardous by the oral route, and indicate that the compound is more acutely toxic than 1,1-dichloroethane, 1,1,1-trichloroethane, pentachloroethane, and hexachloroethane (Patty, 1981). According to a World Health Organization report (1970; cited by Torkelson and Rowe, 1981) rabbits and mice are as susceptible as rats to EDC. Heppel et al. (1945) observed 60% mortality (6 of 10 treated) in mice 10 days after an acute oral dose of 700 mg EDC/kg body weight, which was administered as a 5% solution in olive oil. Similar treatment with 900 mg/kg EDC in 5% olive oil produced mortality in 10/10 mice, but 6/6 survived a dose of 500 mg/kg given as a 10 percent solution in olive oil. Munson et al. (1982) recently determined that the single oral dose LD_{50}'s of EDC for male and female CD-1 mice were 489 and 413 mg/kg, respectively. In these studies, EDC was apparently administered in water solution, and all mice died over a 48-hour period. Gross pathologic examination indicated that the lungs and liver appeared to be the target organs. Dogs and humans may tolerate larger doses. Since EDC causes vomiting, the higher tolerance in dogs and humans is likely attributed to the ability to vomit in these two species. Ristler and Luckhardt (1929) found that oral doses >500 mg/kg tended to be vomited by dogs.

In 2 unanesthetized dogs (weighing 9 and 12.5 kg) administration of 0.63 g/kg EDC by gavage produced initial excitement (8 minutes after treatment)

TABLE 9-24

Effect of Acute Exposure to Ethylene Dichloride

Route	Species	Number	Dose	Effect	Reference
Oral	rats	80	0.68 g/kg	LD_{50}	McCollister et al., 1956
Oral	rats	5/group	0.77 g/kg	LD_{50}	Smyth et al., 1969
Oral	mice	10 10 6	0.90 g/kg (in olive oil) 0.70 g/kg (in olive oil) 0.50 g/kg	10/10 dead 6/10 dead no deaths	Heppel et al., 1945
Oral	mice (CD-1, male)	NS	0.489 g/kg (in water)	LD_{50}	Munson et al., 1982
Oral	mice (CD-1,female)	NS	0.413 g/kg	LD_{50}	Munson et al., 1982
Inhalation	rats	6 male or female Sherman Strain (100-150 weight)	1000 ppm for 4 h	2/6, 3/6 or 4/6 dead in 14 day observation period.	Carpenter et al., 1949
Inhalation	rats (female)	4-6/group	12,000 ppm for 0.1 h 0.2 h 3000 ppm for 0.3 h 0.5 h 1000 ppm for 1.5 h 3.0 h 300 ppm for 3.0 h 5.5 h 200 ppm for 7.0 h	No adverse effects Adverse effect No adverse effect Adverse effect No adverse effect Adverse effect No adverse effect Adverse effect No adverse effect	Spencer et al., 1951

TABLE 9-24 (cont.)

Route	Species	Number	Dose	Effect	Reference
Inhalation	rats	20	3000 ppm for 6 h	20/20 dead	Spencer et al., 1951
		22	3000 ppm for 5 h	22/22 dead	
		40	3000 ppm for 4 h	38/40 dead	
		40	3000 ppm for 3 h	24/40 dead	
		51	3000 ppm for 2 h	6/51 dead	
		44	3000 ppm for 1.6 h	1/44 dead	
		32	3000 ppm for 1.0 h	1/32 dead	
		44	3000 ppm for 0.7 h	1/44 dead	
		22	3000 ppm for 0.5 h	0/22 dead	
		10	1500 ppm for 8 h	7/10 dead	
		30	1500 ppm for 7 h	24/30 dead	
		10	1500 ppm for 6 h	7/10 dead	
		41	1500 ppm for 4 h	2/41 dead	
		24	1500 ppm for 3 h	1/24 dead	
		10	1500 ppm for 2 h	0/10 dead	
		32	1000 ppm for 8 h	20/32 dead	
		31	1000 ppm for 7 h	17/31 dead	
		32	1000 ppm for 6 h	5/32 dead	
		30	800 ppm for 7 h	10/30 dead	
		20	600 ppm for 8 h	4/20 dead	
		33	600 ppm for 7 h	3/33 dead	
		20	600 ppm for 5 h	0/20 dead	
		20	300 ppm for 7 h	0/20 dead	
Inhalation	rats	20	3000 ppm for 7 h	20/20 dead	Heppel et al., 1945
		15	3000 ppm for 3.5 h	15/15 dead	
		15	3000 ppm for 1.5 h	0/15 dead	
		12	1500 ppm for 7 h	4/20 dead	
		13	1500 ppm for 4 h	0/13 dead	
	mice	22	3000 ppm for 7 h	22/22 dead	
		20	1500 ppm for 7 h	20/20 dead	
		23	1500 ppm for 2 h	1/23 dead	
	guinea pigs	14	3000 ppm for 7 h	14/14 dead	
		12	1500 ppm for 7 h	6/12 dead	
	rabbits	16	3000 ppm for 7 h	12/16 dead	
	cats	3	3000 ppm for 7 h	0/3 dead	
	hogs	2	3000 ppm for 7 h	2/2 dead	
	raccoons	2	3000 ppm for 7 h	0/2 dead	

TABLE 9-24 (Cont.)

Route	Species	Number	Dose	Effect	Reference
Intraperitioneal	guinea pig (male)	4/group	150, 300 and 600 mg/kg 1 dose	No effect on liver histology 24 hours after injection. No effect on serum ornithine carbamyl transferase (OCT) activity 24 hours later at 150 or 300 mg/kg. Increased OCT activity at 600 mg/kg; death of 1 animal.	Divincenzo and Krasavage, 1974
Subcutaneous	dogs	6	0.94 or 1.26 g/kg body weight	Death within 24 hours at higher dose; histology: mild perilobular fatty degeneration in liver, swelling of tubular cells and mild hemorrhage in the kidney, lung edema histological changes more marked in dogs. In dogs only: corneal opacity evident by 10 hours; necrosis of corneal endothelium; corneas became clear by fifth day.	Kuwabara et al., 1968
	cats	NS	0.94 or 1.26 g/kg body weight		
	rabbits	NS	0.94 or 1.26 g/kg body weight		
	albino rats	NS	0.94 or 1.26 g/kg body weight		
Subcutaneous	rats	10/group 4/group at the lowest dose	0.38, 0.5, 0.75, 1.0, 1.25 g/kg (in olive oil)	0.75/kg: 50% mortality; 0.38 g/kkg: no deaths	Heppel et al., 1945
Subcutaneous	mice	10/group	0.25, 0.38, 0.75 g/kg (in olive oil)	0.38 g/kg: 80% mortality 0.25 g/kg: no deaths	Heppel et al., 1945

h = hours

followed by decreased excitement. Progressive incoordination and salivation was evident. In 24 minutes, sleep (from which the dogs could be aroused) supervened for another 20 minutes, at which time depression was relieved. Vomiting occurred subsequently, after which signs of recovery were evident (Kistler and Luckhardt, 1929). Larger doses of 1.26 g/kg in 2 dogs, 1.89 g/kg in one dog, and 2.51 g/kg in two dogs produced similar symptoms of greater severity. Vomiting occurred earlier after administration of the compound; little food or water was ingested and vomiting persisted in one dog that received 1.26 g/kg EDC. The corneas of the eyes in all five animals were opaque within 24 hours.

9.2.2.1.2. Dermal Exposure -- Skin absorption LD_{50} values of 4.9 g/kg (Torkelson and Rowe, 1981) and 2.8 g/kg (Torkelson and Rowe, 1981) have been determined with rabbits. Strong erythema, edema, or slight necrosis was produced upon application of 0.01 mℓ of undiluted EDC to the uncovered rabbit belly (Smyth et al., 1969).

9.2.2.1.3. Inhalation Exposure -- Sayers et al. (1930, cited in Browning, 1965 and NIOSH, 1976) reported that death occurred in guinea pigs within a few minutes of exposure to 100,000 ppm EDC, and on the day following exposure to 10,000 ppm EDC for 25 minutes. Progressive signs of intoxication were observed in groups of 3 or 6 guinea pigs that were exposed to EDC at concentrations ranging from 600 to 60,000 ppm for durations up to 8 hours. One third of each group was sacrificed immediately after exposure, another one-third sacrificed after 4 days of exposure and the final one-third was sacrificed at the end of the eighth post-exposure day unless death supervened. The signs of intoxication (squinting and lacrimation of the eyes and rubbing of the nose, vertigo, static and motor ataxia, retching movements, unconsciousness, incoordination of extremities, and marked changes in respiration) appeared in less than 10 minutes, and death occurred in 30 minutes, after exposure to 60,000 ppm EDC.

Exposure to a lower concentration (10,000 ppm) for 15 to 20 minutes produced these symptoms in 25 minutes and delayed death a day or more after exposure. No mortality or signs of intoxication occurred in guinea pigs exposed to 1200 ppm for 8 hours.

Congestion and edema of the lungs and generalized passive congestion of the visceral organs were observed in animals that died during exposure (Sayers et al., 1930, cited in NIOSH, 1976). In animals sacrificed immediately after exposure, congestion of the liver, spleen, lungs, and kidneys was observed. Pulmonary congestion, pulmonary edema and renal hyperemia were seen in those animals that died 1 to 8 days after exposure, and the renal and lung effects were more pronounced in the animals sacrificed 3 to 4 days post-exposure than in those sacrificed immediately after exposure. Partial resolution of visceral effects were observed by 8 days after exposure. In these studies, the severity of pathological changes was dependent on duration and concentation of exposure.

Heppel et al. (1945) reported that a single exposure to 3000 ppm EDC (12.4 mg/ℓ) for 7 hours produced death in all of 14 treated guinea pigs within 3 days of exposure. The guinea pigs were inactive and breathing was labored after exposure. Microscopic examination of 11 guinea pigs revealed congestion in the liver, lung and adrenal glands. Focal necrosis of the adrenal cortex in 5 of the guinea pigs, and slight to moderate fatty degeneration of renal tubular epithelium was noted in 8 of the animals. In another group of 8 guinea pigs similarly exposed to 3000 ppm EDC, fatty infiltration of the myocardium was observed in all of 7 animals that were examined histologically. Changes in the lung, kidney and adrenal cortex, similar to those observed in the first group of animals were also found.

Heppel et al. (1945) also found that inhalation exposure to 3000 ppm EDC (12.4 mg/ℓ) for 7 hours was fatal to rats, mice and rabbits within 3 days of exposure. Varying degrees of narcosis were observed in the animals during exposure, and dyspnea and increasing weakness preceded death. Pulmonary congestion, mild to moderate degeneration of renal tubular epithelium and liver, and occasional necrosis of the adrenal cortex were observed at autopsy; congestion of the spleen was additionally found in rats. Inhalation of 3000 ppm EDC for 7 hours was fatal for 2 hogs but was not fatal for 2 raccoons or 3 cats. Reduction of dose by exposure to one-half the concentration of EDC (1500 ppm) for a similar duration (7 hours) was lethal to 6 of 12 guinea pigs and to less than one-fifth of the rats (4 of 20). This lower dose was fatal, however, to all of a group of 20 mice. Reduction of the duration of exposure in rats to 4 hours and mice to 2 hours decreased mortality (Heppel et al., 1944).

Spencer et al. (1951) subjected groups of 4 to 6 female rats to varying concentrations of EDC (200, 300, 1000, 3000 or 12,000 ppm) for varying durations to determine the doses and durations of single exposures that produced and did not produce adverse effects. No-adverse effect exposures ranged from 200 ppm (0.8 mg/ℓ) for 7 hours to 12,000 ppm (48.6 mg/ℓ) for 0.1 hours. Doubling the duration of exposure at 12,000 ppm produced adverse effects. Exposure to 3000 ppm EDC for 0.3 hours was without effect, but increasing the duration of exposure to 0.5 hours caused adverse effects.

Spencer et al. (1951) also sacrificed groups of 10-54 rats after inhalation exposure to EDC at concentrations ranging from 300 to 20,000 ppm for durations of 8.0 to 0.1 hours. A decrease in body weight, increase in liver and kidney weight, increase of blood urine nitrogen, increase of plasma prothrombin clotting time, decrease in serum phosphatase, increase in liver lipids and histological changes in the kidneys, liver and adrenal glands were observed. The kidney changes consisted of tubular damage that ranged from slight parenchymatous degeneration of the epithelium to complete necrosis accompanied by interstitial edema, congestion and hemorrhage. Changes ranging from slight congestion and slight parenchymatous degeneration to marked hemorrhagic necrosis were observed in the liver. Some parenchymatous degeneration of the adrenal cortex was found in the most severely affected animals. Pulmonary congestion and edema was observed at concentrations above 3000 ppm. Carpenter et al. (1949) reported an inhalation LC_{50} in rats to be 1000 ppm in air for a 4-hour exposure.

9.2.2.1.3.1 Central Nervous System and Cardiovascular System. Inhalation of 3000 ppm EDC (12.4 mg/ℓ) for 7 hours in five species (rabbits, guinea pigs, hogs, rats and mice) produced varying degrees of narcosis (Heppel et al., 1945). Spencer et al. (1951) partially attributed the inactivity or stupor and a slower response to handling in rats, at vapor concentrations of 3000 ppm and lower, to toxic injury to organs other than depression of the central nervous system. At concentrations of 12,000 ppm and lower varying degrees of "drunkenness" were attributed to depression of the central nervous system. Considerable depression of the central nervous system was produced at 22,000 ppm causing death in rats within 0.4 hours. Animals that died from exposure to 20,000 ppm EDC were in a state of deep anesthesia during the period of exposure. At all vapor concentrations a large proportion of the rats died suddenly after leaving the exposure chamber. Marked cyanosis, reduced body temperature, stupor or coma, and failing respiration were observed. Spencer et al. (1951) hypothesized that this response is suggestive of cardiovascular collapse. Other deaths, which occurred over a period of two to seven days, were accompanied by loss in body weight and other signs of toxicity; the authors attribute these deaths to renal injury.

Inhalation of EDC (0.1 to 5 cc, introduced by volatilization into a Jackson Carbon Dioxide Absorption Apparatus) produced a drop in blood pressure, depression of the knee jerk reflex and stimulation followed by a short cessation of respiration in sodium barbital anesthetized dogs (number unspecified) (Kistler and Luckhardt, 1929). These dogs had been subjected to spinal cord transection prior to EDC treatment. Similar effects on blood pressure and the knee jerk were observed in sodium barbital anesthetized dogs (11-20 kg) after intravenous injection of amounts as small as 0.1 cc, while 0.3 cc caused a cessation of respiration for a duration of up to 40 seconds.

9.2.2.1.3.2. Eyes. Inhalation of EDC was observed to produce a clouding of the cornea in dogs and foxes, but not in rabbits, guinea pigs, mice, rats, hogs, raccoons, chickens or cats (Heppel et al., 1944). A single exposure to a vapor concentration of 1000 ppm for 7 hours produced turbidity in the eyes of dogs (Table 9-25). A higher concentration of 3000 ppm caused turbidity in the cornea of the red fox after a single exposure of 7 hours duration. Repeated exposure interspersed with two days of no exposure at a lower concentration of 400 ppm produced clouding in the cornea of six dogs, which cleared during the days free of exposure. Development of resistance to toxic effects in the cornea after repeated exposure was observed.

Corneal opacity was also observed within 10 hours in 6 dogs that received a subcutaneous injection of 0.94 g/kg EDC (Kuwabara et al., 1968) (Table 9-25). Marked swelling of most of the endothelial cells of the cornea was seen at 12 hours, and the reparative process was found to occur by 24 hours. Similar corneal changes were produced in dogs, rabbits and cats when EDC (a 1% suspension dissolved in mineral oil and homogenized in 0.5% gelatin solution) was instilled directly into the anterior chamber of the eye. The authors suggested that the apparent vulnerability of the dog eye to EDC by routes other than direct local application was due to "a greater amount of dichloroethane coming in contact with the dog endothelium rather than an unusual susceptibility of the eye itself."

TABLE 9-25

Effect of Ethylene Dichloride on the Cornea

Route	Species	Number of Animals	Dose	Effect	Reference
Inhalation	rabbits	16	3000 ppm for 7 h 1 exposure	No effect on eyes	Heppel et al., 1944
	guinea pigs	14			
	mice	19			
	rats	20			
	hogs	2			
	raccoons	2			
	cats	2			
Inhalation	red fox	1	3000 ppm for 7 h 1 exposure	Loss of appetite; barely detectable turbidity in eyes within 6 h; eyes were opaque 2 d later; death 6 d after exposure.	Heppel et al., 1944
Inhalation	red fox	1 (same animal as tested above)	1500 and 1000 ppm for 7 h 1 exposure at each concentration	No adverse effect on eyes	Heppel et al., 1944
	raccoon	2			
Inhalation	dog	6	1500 ppm for 7 h, 1 exposure	No effect on cornea of 1; faint turbidity in eye of 1; intense clouding of both corneas in 4; histology; corneal edema, degeneration of corneal epithelium, infiltration of polymorphonuclear leucocytes into substantia propria.	Heppel et al., 1944

TABLE 9-25 (Cont.)

Route	Species	Number of Animals	Dose	Effect	Reference
Inhalation	dog	10	1000 ppm for 7 h, 1 exposure	Symmetric turbidity in the corneas of 8; up to 3 weeks required for partial regression.	Heppel et al., 1944
Inhalation	guinea pigs	NS	1500 ppm for 7 h, repeated exposure	Death in most animals after 4 exposures; no adverse effect on eyes.	Heppel et al., 1944
	rats	NS			
	rabbits	NS			
Inhalation	dog	3	1500 ppm for 7 h, repeated exposure	Intense bilateral corneal opacity in both eyes 48 h after first exposure; death after 5, 6 or 30 exposures. Turbidity in eyes retained throughout.	Heppel et al. 1944
Inhalation	dog	10	1000 ppm for 7 h, 5 d/wk, repeated exposure, length NS	Increasing turbidity of cornea during 5 exposure days, clearing during 2 non-exposure days; increased tolerance with successive bouts of exposure; complete resistance of cornea finally.	Heppel et al., 1944
Inhalation	cats	NS	1000 ppm for 7 h, 5 d/wk, repeated exposure, length NS	No adverse effects in eyes	Heppel et al., 1944
	monkeys				
	chickens				
	rodents (species, NS)				

TABLE 9-25 (Cont.)

Route	Species	Number of Animals	Dose	Effect	Reference
Subcutaneous	dogs (puppies and adults)	6	0.94 g/kg	Corneal opacity evidence within 10 hours; necrosis of corneal endothelium; clearing by fifth day.	Kuwabara et al., 1968
	cats	NS	0.94 g/kg	No effect on cornea	Kuwabara et al., 1968
	rabbits	NS	0.94 g/kg	No effect on cornea	Kuwabara et al., 1968
	albino rats	NS	0.94 g/kg	No effect on cornea	Kuwabara et al., 1968
Inhalation	dogs	6	400 ppm for 7 h, 5 d/wk, for 10 weeks	Mild clouding during first week, cleared during 2 non-exposure days; 5th week of exposure; faint opacity of cornea 10th week of exposure: no trace of turbidity.	Heppel et al., 1944

h = hour; d = day; wk = week

9.2.2.2. SUBCHRONIC AND CHRONIC EXPOSURE

9.2.2.2.1. Oral Exposure -- EDC has been tested for carcinogenicity in an NCI bioassay with Osborne-Mendel rats and B6C3F1 mice (NCI, 1978). The compound was administered at time-weighted average doses of 95 and 47 mg/kg (rats of both sexes), 195 and 97 mg/kg (male mice) and 299 and 149 mg/kg (female mice) for a period of 78 weeks, according to the regimen described in Section 9.5. Fifty animals of each sex were treated/dose level, and the animals were observed for an additional 28 weeks (rats) or 12-13 weeks (mice) after pretreatment.

As detailed in Section 9.5, no distinct dose-related mean body weight depression was apparent in either male or female rats relative to vehicle controls. Mortality was, however, early and severe in many of the dosed rats, particularly those given the highest dose. Mean survival was ≈55 weeks for the high-dose males and females. Toxic rather than carcinogenic effects of EDC appeared to be responsible for the deaths. No distinct, dose-related mean body weight depression was observed in male mice or in low-dose female mice, but mean body weight depression for high-dose female mice was apparent as early as the 15th week of treatment. A significant positive association between increased dosage and elevated mortality was found for female mice; 72% (36/50) of the females died between weeks 60 and 80. The presence of one or more tumors in these mice suggests that these deaths may have been tumor related. There was no statistically significant association between dosage and mortality for male mice.

Munson et al. (1982) evaluated the effect of subchronic 14-day and 90-day oral EDC exposures on the immune response of male CD-1 mice. EDC was administered daily by gavage in the 14-day study at levels of 4.9 and 49 mg/kg, which represent 0.01 and 0.1 times the single dose LD_{50} determined in a preliminary study (Section 9.2.2.1.1). For the 90-day study, EDC was administered in the drinking water at levels intended to be equivalent to those administered by gavage; in addition, a 10-fold higher dose was added because the results of the 14-day exposure indicated that doses >49 mg/kg could be tolerated. The calculated time-weighted average doses of EDC delivered in the 90-day study based on actual fluid consumed were reported to be 3, 24 and 189 mg/kg. Results of standard toxicological analyses showed that body weight was unaltered during the 14-day study, but that EDC did elicit a dose-dependent decrease in growth rate and fluid consumption when administered over 90 days. Thirty-two mice per dose were weighed in the 90-day study but the numbers weighed in the 14-day study were not stated. EDC did not alter the weights of selected organs (liver, spleen, lungs, thymus, kidneys, brain) in either of the studies. It was further found that exposure to 49 mg/kg/day EDC caused a 30% decrease in leukocyte number in the 14-day study, although the number of leukocytes was normal after 90 days of exposure. Other hematologic parameters (hematocrit and hemoglobin evaluated after 14 or 90 days, erythrocytes and platelets evaluated after 90 days), coagulation values (fibrinogen and prothrombin time evaluated after 14 days), and clinical chemistry parameters (lactic dehydrogenase, serum glutamic-pyruvate transaminase and blood urea nitrogen evaluated after 14 days) were unaltered by EDC exposure. The hematological/coagulation/clinical chemistry parameters were assessed in 10-12 and 16 mice/dose in the 14-day and 90-day studies, respectively.

The status of the humoral immune system was determined by measuring the number of IgM spleen antibody-forming cells (AFC) to sheep erythrocytes (sRBC) after 14 and 90 days, the serum antibody level to sRBC after 90 days, and the lymphocyte response to the B-cell mitogen LPS (lipopolysaccharide from Salmonella typhosa 0901) after 90 days (Munson et al., 1982). Results of assays with 10-12 mice (14 days) and 16 mice/dose showed that EDC produced a significant ($P<0.05$) reduction in AFCs at 4.9 and 49 mg/kg in the 14-day study (25 and 40% suppression, respectively), but that EDC exposure for 90 days caused no significant ($P<0.05$) change in the number of AFC spleen cells (although there was an indication of suppression at 189 mg/kg/day). There also appeared to be an EDC dose-dependent reduction in hemagglutination titer after 90 days, although this response was not significant at the $p<0.05$ level. EDC did not alter the spleen cell response to three concentrations of LPS. Cell-mediated immunity was assessed by measuring the delayed hypersensitivity response (DTH) to sRBC and the response to the T-lymphocyte mitogen, concanavalin A. EDC produced a slight but significant ($P<0.05$) non-dose-dependent inhibition at both 4.9 and 49 mg/kg in the 14-day study, but 90-day exposure did not alter DTH response or spleen lymphocyte response to concanavalin A. EDC did not alter the functional activity of the reticuloendothelial system, as measured by the vascular clearance rate and tissue (i.e., liver, spleen, lungs, thymus or kidneys) uptake of ^{51}Cr after 90 days. Dexamethasone was used as a positive control in the above studies. Results of similar tests with female mice were not presented, but reportedly were not remarkably different from the males.

The results of the above experiments (Munson et al., 1982) indicate that EDC produced a suppression of both humoral and cell-mediated immunity when administered daily for 14 days by stomach tube, but not when consumed in the drinking water for 90 days (although there were trends toward suppression at the high exposure level). Two explanations were offered for these results. First, the effective dose at the immunocompetent cell may be higher with the bolus presentation than with the semi-continuous self-administration in the drinking water. Second, EDC may induce its own metabolism over the longer exposure period, thereby effectively reducing the amount of chemical reaching the immune cells.

9.2.2.2.2. Inhalation Exposure -- Four animal species (15 rats of both sexes, 8 guinea pigs of both sexes, 2 male and 1 female rabbits, and 2 male monkeys) were exposed to EDC vapor at levels of 400 ppm (1.62 mg/ℓ) and 100 ppm (0.405 mg/ℓ) for 7 hours daily, 5 days/week for 6 months (Spencer et al., 1951). In addition, 15 rats of both sexes and 8 guinea pigs of both sexes were similarly exposed to 200 ppm EDC (0.81 mg/ℓ) for 151 and 180 7-hour periods, respectively. Repeated exposure at 100 ppm did not produce adverse effects in any of the four species as determined by general appearance and behavior, mortality, growth, body and organ weights, and gross and microscopic examination of tissues (Table 9-26). No adverse effects were indicated by periodic hematological examination of the treated rats, guinea pigs, or rabbits. Exposure to 200 ppm EDC did not produce any adverse effects in the rats, but did elicit slight parenchymatous degeneration of the liver with a few diffusely distributed fat vacuoles in half of the guinea pigs. A slight increase of total lipid, phospholipid, neutral fat and free and esterified chloresterol was also found in the guinea pigs exposed to 200 ppm EDC, and the final body weights of the treated male guinea pigs were significantly different from control animals. Severe toxic effects were found in the rats, guinea pigs, and monkeys that were exposed to 400 ppm EDC (1.62 mg/ℓ) (see Table 9-26). The three rabbits that were exposed to 400 ppm EDC were not adversely affected, although Heppel et al. (1946) reported a high mortality in rabbits exposed to this concentration of EDC.

Heppel et al. (1945) exposed rats, mice, rabbits, guinea pigs, hogs and dogs to 1500 ppm EDC (6.4 mg/ℓ). Almost all of these animals died before 6 daily exposures of 7 hours each were completed. Hemorrhaging in the lungs, gastrointestinal tract and adrenals; fatty degeneration of the myocardium; degeneration within the renal tubules; and congestion of the liver and intestines were found at autopsy.

TABLE 9-26

Effect of Subchronic Exposure to Ethylene Dichloride

Route	Species	Number	Dose	Effect	Reference
Inhalation	rats	26 (average weight: 198 g)	1000 ppm (3.0 mg/ℓ) 7 h/d x 5 d/wk	20 dead within 15 exposures; progressive weakness culminating in inability to stand. Histology of 4 rats: degeneration and proliferation changes in renal tubular epithelium; chronic splenitis in 20 rats; pulmonary congestion in 2 rats.	Heppel et al., 1946
Inhalation	rabbits	6 (average weight: 2480 g)	1000 ppm (3.9 mg/ℓ) 7 h/d x 5 d/wk	5 dead within 43 exposures survivor exposed 64 days	Heppel et al., 1946
Inhalation	guinea pig	15 (average weight: 161 g)	1000 ppm (3.9 mg/ℓ) 7 h/d x 5 d/wk	10 dead within 2 exposures	Heppel et al., 1946
	guinea pig	10 (average weight: 558 g)	1000 ppm (3.9 mg/ℓ) 7 h/d x 5 d/wk	10 dead within 2 exposures	Heppel et al., 1946
	guinea pig	16 (average weight: 900 g)	1000 ppm (3.9 mg/ℓ) 7 h/d x 5 d/wk	16 dead within 4 exposures lacrimation and marked inactivity during exposure; congestion of lung, liver, heart, kidney, adrenal gland and spleens.	Heppel et al., 1946
Inhalation	dogs	6 (7000-8300 g)	1000 ppm (3.9 mg/ℓ 7 h/d x 5 d/wk	1 dead after 30 exposures 1 dead after 43 exposures	Heppel et al., 1946

TABLE 9-26 (Cont.)

Route	Species	Number	Dose	Effect	Reference
Inhalation	rats	15 male 1 female (average weight: 167 g)	400 ppm (1.54 mg/ℓ) for 7 h/d x 5 d/wk for 60 exposures	Total dead: 9 (6 dead after 4 exposures) Histology in 6 survivors: no changes in 5; diffuse myocarditis and fatty degeneration of liver, kidney and heart in 1.	Heppel et al., 1946
		23 controls	0	1 dead. Histology: no change.	
Inhalation	guinea pigs	18 male 2 female (average weight: 303-737)	400 ppm (1.54 mg/ℓ) for 7 h/d x 5 d/wk	13 dead after 45 exposures 1 dead after 65 exposures Histology in 10: fatty degeneration of liver and kidney in 4 dead; fatty degeneration of heart in 2 dead; no histological change in 6 survivors of exposure.	Heppel et al., 1946
		30 controls	0	3 deaths.	
Inhalation	rabbits	2 male 3 female (average weight: 3110 g)	400 ppm (1.54 mg/ℓ) for 7 h/d x 5 d/wk	All dead after 97 exposures. No hematological changes.	Heppel et al., 1946
		4 controls	0	No deaths.	
Inhalation	dogs	3 male puppies (average weight: 1330 g) 6 female adult (average weight: 9100 g)	400 ppm (1.54 mg/ℓ) for 7 h/d x 5 d/wk for 167-177 exposures	No deaths; 6 adults: no effect on mean arterial pressure, bromsulfalein excretion rate, prothrombin time, plasma total protein, albumin, globulin, non-protein nitrogen, icterus index, urine; slight fatty change in livers of 5 and kidney of 1.	Heppel et al., 1946
		4 controls	0	No deaths.	

TABLE 9-26 (Cont.)

Route	Species	Number	Dose	Effect	Reference
Inhalation	cats	6 (2660 g average weight)	1000 ppm (3.9 mg/ℓ) 7 h/d x 5 d/wk	2 dead after 43 exposures congestion and fatty metamorphosis in liver of all.	Heppel et al., 1946
Inhalation	monkeys	2 (4880 g average weight)	1000 ppm (3.9 mg/ℓ) 7 h/d x 5 d/wk	1 dead after 2 exposures 1 dead after 43 exposures; fatty degeneration of liver and slight fatty changes in kidney; focal myocarditis in 1 monkey.	Heppel et al., 1946
Inhalation	cats	4	500 ppm 6 h/d x 5 d/wk for 6 wks	No deaths; dilated hearts; blood urea nitrogen increased to 114 mg/100 mℓ.	Hoffmann et al., 1971
Inhalation	rabbits	4	500 ppm 6 h/d x 5 d/wk for 6 wks	3/4 dead after 10-17 exposures; dilated hearts.	Hoffman et al., 1971
Inhalation	guinea pigs	10	500 ppm 6 h/d x 5 d/wk for 6 wks	9/10 dead after 4-14 exposures; apathy and weight loss, fatty degeneration and necrosis of myocardium, liver, kidney and adrenals.	Hoffman et al., 1971
Inhalation	rats	10	500 ppm 6 h/d x 5 d/wk for 6 wks	All dead after 1-5 exposures; hyperemia of lungs; fatty degeneration and necrosis of myocardium, liver, kidney, and adrenals.	Hoffman et al., 1971

TABLE 9-26 (Cont.)

Route	Species	Number	Dose	Effect	Reference
Inhalation	rats	1 male Wistar 11 female Wistar (average weight: 249 g)	200 ppm (0.73 mg/ℓ) 7 h/d x 5 d/wk	7 dead; 1 after 73 exposures, 6 after 44 exposures. Symptoms: weight loss; listless; crusting of eyes. Histology of 5 rats killed after 86 exposures: fatty degeneration of kidney in 1 rat; no other changes noted in liver, heart, lungs, kidney, adrenals and spleen; no effect on red and white blood cell count, hemoglobin and differential counts (7 treated compared with 6 control rats).	Heppel et al., 1946
		14 controls	0	1 dead.	
Inhalation	mice	20	200 ppm (0.73 mg/ℓ) 7 h/d x 5 d/wk	18 dead after 7 exposures.	Heppel et al., 1946
Inhalation	guinea pigs	12 male, 2 female (average weight: 376 g)	200 ppm (0.73 mg/ℓ) 7 h/d x 5 d/wk	4 dead after 88 exposures; 1 dead after 115 exposures. Histology of 9 guinea pigs killed after 124 exposures: pulmonary congestion in 4, liver necrosis in 1, necrosis of adrenal cortex in 1.	Heppel et al., 1946
		18 controls	0	1 dead. Histology of 5 guinea pigs: fatty liver and myocardium of 2; no other changes noted in liver, heart, lung, kidneys, adrenals and spleen.	

TABLE 9-26 (Cont.)

Route	Species	Number	Dose	Effect	Reference
Inhalation	rabbits	5 (average weight: 2720)	200 ppm (0.73 mg/ℓ) 7 h/d x 5 d/wk	No deaths. No histological changes found; no effect on red and white blood cell count, hemoglobin, and differential counts compared with controls.	Heppel et al., 1946
		4 controls	0	No deaths.	
Inhalation	monkeys	2 males (average weight: 8740 g)	200 ppm (0.73 mg/ℓ) 7 h/d x 5 d/wk for 125 exposures	No deaths Histology of both: focal calcification in adrenal medulla of 1; fatty droplets in liver and myocardium of both.	Heppel et al., 1946
		no controls			
Inhalation	rats	15 male, 15 female	200 ppm (0.81 mg/ℓ) 7h/d, 5 d/wk for 151 exposures	No adverse effects on general appearance, behavior, growth, mortality, final body and organ weights, hematology, gross and microscopic histology.	Spencer et al., 1951
Inhalation	guinea pigs	8 male, 8 female	200 ppm (0.81 mg/ℓ) 7 h/d, 5 d/ wk for 180 exposures	Final body weight significantly different from controls in males, and growth less than controls, but not sigificant in females. Significant increase in male liver weights only; slight parenchymatous hepatic degeneration in half of guinea pigs of both sexes; no effect on hematology; slight increase in trial lipid, phospholipid, neutral fat, free and esterified cholesterol.	Spencer et al., 1951

TABLE 9-26 (Cont.)

Route	Species	Number	Dose	Effect	Reference
Inhalation	rats	15 male, 15 female	100 ppm (0.405 mg/ℓ) 7 h/d, 5 d/wk males: 151 exposures females: 142 exposures	No adverse effect on general appearance, behavior, mortality, growth, final body and organ weights, hematology, gross and microscopic histology, BUN, blood non-protein nitrogen, serum phosphatase, plasma prothrombin clotting time, total levels lipid, phospholipids, neutral fat in liver, free and esterified cholesterol in liver.	Spencer et al., 1951
Inhalation	guinea pigs	8 male, 8 female	100 ppm (0.405 mg/ℓ) 7 h/d, 5 d/wk males: 121 exposures females: 162 exposures	No adverse effect on mortality, growth, final body and organ weights, BUN, blood non-protein nitrogen, serum phosphatase, plasma prothrombin clotting time, gross and microscopic histology, total liver lipid phospholipids, neutral fat in liver, free and esterified cholesterol in liver.	Spencer et al., 1951
Inhalation	rabbits	2 male, 1 female	100 ppm (0.405 mg/ℓ) 7 h/d, 5 d/wk for 178 exposures	No adverse effect on appearance, behavior, growth, final body and organ weights, gross and microscopic histology, hematology.	Spencer et al., 1951
Inhalation	monkeys	2 male	100 ppm (0.405 mg/ℓ) 7 h/d, 5 d/wk for 148 exposures	No adverse effect on appearance, behavior, growth, final body and organ weights, gross and microscopic histology, hematology.	Spencer et al., 1951

TABLE 9-26 (Cont.)

Route	Species	Number	Dose	Effect	Reference
Inhalation	rats	16 female 23 male	100 ppm (0.42 mg/ℓ) 7 h/d x 5 d/wk for 4 months	No deaths, no effect on rate of growth in 15 males compared with 15 male controls. 15 of 16 females became pregnant; rat pups were unaffected by exposure. No histological effects in liver, heart, lungs, kidney, adrenal glands and spleen of 10 rats examined.	Heppel et al., 1946
Inhalation	guinea pigs	10 male 6 female	100 ppm (0.42 mg/ℓ) 7 h/d x 5 d/wk for 4 months	2 dead (disease of neck with enlarged caseous glands) No histological effects in liver, heart, lungs, kidney, adrenal glands and spleen of 10 animals examined.	Heppel et al., 1946
		30 control	0	3 dead (disease of neck with enlarged caseous glands).	
Inhalation	mice	19 juveniles	100 ppm (0.42 mg/ℓ) 7 h/d x 5 d/wk for 19 exposures	No deaths; no effect on weight gain.	Heppel et al., 1946
Inhalation	cats rabbits guinea pigs rats	4 4 10 10	100 ppm 6 h/d x 5 d/wk for 17 wks	No clinical symptoms No effect on serum levels of creatinine, urea, SGOT, SGPT, on body weight. No changes in liver, kidney, and other organs (not specified).	Hoffman et al., 1971

h = hour; d = day; wk = week

BUN = Blood urea nitrogen

In another study, Heppel et al. (1946) found that repeated exposure (7 hours/day, 5 days/week) to 1000 ppm EDC elicited death in most of the exposed rats, rabbits, guinea pigs, dogs, cats and monkeys (see Table 9-26). Rats, rabbits and guinea pigs appeared to be more susceptible than the other species tested. Pathological changes, which were varied, included congestion of lung, liver, heart, kidney, adrenal gland and spleen in guinea pigs; congestion and fatty metamorphosis in the liver of all exposed cats; renal changes in exposed monkeys and rats; and pulmonary congestion in a few rats. Chronic splenitis occurred in all rats exposed to repeated inhalation of 1000 ppm EDC. Focal myocarditis was found in one monkey. Similar repeated exposures to 400 ppm EDC produced high mortality in rabbits, rats, and guinea pigs (see Table 9-26), but mortality was not observed in 9 dogs subjected to from 167 to 177 exposures at this concentration. No changes were observed in a variety of clinical parameters that were assessed in 6 adult dogs, although slight fatty changes were noted in the livers of five and the kidney of one of the dogs. Rat and guinea pig survivors of 400 ppm EDC exposure did not exhibit histological changes with the exception of 1 of 6 rats that exhibited diffuse myocarditis and fatty degeneration of the liver, kidney and heart. Repeated inhalation exposure to 200 ppm EDC produced mortality in mice, rats and guinea pigs, but not in rabbits or monkeys (see Table 9-26). Pathologic effects of exposure to 200 ppm EDC included a few cases of pulmonary congestion, fatty degeneration in the kidney of one rat, necrosis of the liver and adrenal cortex in one guinea pig, and fatty droplets in the liver and myocardium of both monkeys. No clinical or histopathological effects were observed in 39 rats or 16 guinea pigs exposed to 100 ppm EDC for 4 months or in 19 juvenile mice exposed to this level of EDC for 19 exposures.

Hoffman et al. (1971) exposed groups of 4 cats, 4 rabbits, 10 guinea pigs and 10 rats to 500 or 100 ppm EDC for 6 hours/day, 5 days/week for 6 weeks.

Mortality from exposure to 500 ppm EDC was high (see Table 9-26). Variable changes in the heart, lungs, liver, kidney, and adrenals were found at autopsy. No toxic effects were observed in the exposed animals at 100 ppm. An elevation of BUN and creatinine was noted in 1/4 rabbits, but the significance of these changes is uncertain. The exposed cats did not grow as well as the control cats.

The effect of EDC on blood elements and on renal and liver function was investigated using groups of 10 rabbits that were exposed to 3000 ppm for 4 hours, or to 3000 ppm for 2 hours/day, 5 days/week for 90 days (Lioia, 1959a,b,c,d). The only significant changes observed after the acute 4-hour exposure were granulations in about 20% of the granulocytes. Varying degrees of anemia accompanied by leukopenia and thrombocytopenia and frequent hyperplasia of granuloblastic and erythroblastic parenchyma in the bone marrow were observed after subchronic exposure. There was also a reduction in leukolipids, but no change in polysaccharides, peroxidase, or ribonucleic acid. In tests for liver function, a decrease in albumin-globulin ratio, a slightly elevated BSP retention, slightly elevated values in colloidal tests (cadmium and cholesterol), and normal Van den Berg (indicating an absence of elevated serum bilirubin) and blood amino acid levels were observed. Measurement of creatinine clearance, portal blood flow, and glomerular filtration rate indicated altered renal function. Congestion, vascular degeneration and small necrotic areas were found in livers and kidneys.

Dimitrieva and Kuleshov (1971) examined the effect of EDC on brain activity in 18 albino rats exposed to 1235 ppm EDC (5 mg/ℓ) for 3.5 months. The duration, frequency and number of exposures were not reported. Electroencephalograms were recorded before exposure and at monthly intervals thereafter from silver and platinum electrodes implanted in the brains of the test animals. The stimulus was composed of an arhythmic photic stimulus of constant intensity and pulse ments were started at 3 months of age, and the 12 month determination was made with animals that were exposed from 14 months of age.

The results suggest that long-term inhalation exposure of one year or longer to EDC at levels of 150 ppm do not produce marked toxicity in rats exposed from 3 months of age (Spreafico et al., 1981). There were no statistically significant changes between treated and control animals with respect to circulating levels of red blood cells, total white blood cell numbers, platelet numbers, relative percentages of lymphocytes, granulocytes and monocytes, and circulating protein levels. Percent albumin values were significantly increased in both sexes at 3 and 18 months but not at 6 months, but no clear dose-response relationship was apparent. Gamma globulin percentages were significantly lower at 3 months in the 150 ppm EDC group. Although changes were not apparent at 6 months, at 18 months there was a significant decrease observed only at 5 and 10 ppm.

No treatment related effects were found on levels of γ-glutamyl transpeptidase (γ-GT), serum glutamic-oxalacetic transaminase (SGOT), serum glumatic-pyruvic transaminase (SGPT), serum alkaline phosphatase, bilirubin or cholesterol (Spreafico et al., 1981). A slight, but not significant, increase in creatine phosphokinase (CPK) level was seen at 18 months in males exposed to 50 and 150 ppm EDC. Lactic acid dehydrogenase (LDH) levels were significantly elevated after 3 months of exposure in both treated male and female groups, but a dose-response relationship was apparent only in males. At 6 months, there was an insignificant increase in LDH levels. At 18 months, significantly higher LDH levels were observed only in males exposed to 5, 50 and 150 ppm EDC without an apparent dose-response relationship. No clear changes were observed for BUN levels, serum glucose levels or uric acid levels (Spreafico et al., 1981).

No consistent and significant differences in a battery of urinary tests (pH, proteins, bilirubin, glucose, hemoglobin, erythrocytes, leukocytes, epithelial duration. A maintained frequency of activity was observed in the EEG of the treated rats. A progressive diminution of amplitude of vacillations occurred, with the amplitude of delta rhythms reaching 50-70 MV (amplitude of delta rhythm before exposures was not specified) while the amplitude of beta rhythm decreased to 10 to 15 MV (amplitudes of pre-exposure beta rhythms were 30 to 80 MV). A loss of ability to assimilate an imposed rhythm was observed by the authors.

The results of an inhalation bioassay for carcinogenesis with Sprague-Dawley rats and Swiss mice have been published (Maltoni et al., 1981). The experimental design and results of these assays are detailed in Section 9.5, but it should be noted that exposure to 250 to 150 ppm, 50, 10 or 5 ppm EDC for 7 hours/day, 5 days/week for 78 weeks elicited no treatment-related changes in body weight or survival ability in rats of either sex or male mice. There was, however, decreased survival ability in female mice exposed to the high level, of EDC. The animals exposed to 250 ppm at the onset of the study exhibited signs of toxicity (i.e., ruffling of hair, hypomotility and loss of muscle tone), prompting dose decrease to 150 ppm after several weeks. Systemic pathological examinations were performed on all the major organs of all animals with or without pathological changes, but the only non-neoplastic histologic effects reported were some "regressive" changes in the liver and adrenal glands that were not dose-related (Cox, 1982).

In a related study with Sprague-Dawley rats, Spreafico et al. (1981) investigated the effect of inhalation exposure to identical levels of EDC (250 to 150, 50, 10 and 5 ppm) on blood clinical chemistry parameters. Histological examinations were not performed on the rats exposed to EDC in this study. Eight to 10 animals per dose level were sacrificed after 3, 6, 12, or 18 months of 7 hours/day, 5 days/week exposure. Rats used for the 3, 6 and 18 month measure-cells, casts, cystals, mucus and microorganisms) were observed after 18 months of inhalation exposure (Spreafico et al., 1981).

Changes in liver and kidney function were indicated, however, in rats exposed to EDC at 14 months of age. SGPT levels were significantly increased in rats of both sexes exposed to 50 and 150 ppm. γ-GT levels were significantly elevated in females treated with 50 and 150 ppm. SGOT levels were significantly elevated at the two lower doses (5 and 10 ppm), and significant decreases were observed at the 2 higher doses (50 and 150 ppm). Cholesterol levels were significantly lower at 50 and 150 ppm in both sexes, but there were no significant changes in bilirubin, CPK, alkaline phosphatase, LDH or glucose levels. Significantly higher levels of uric acid were found at 50 and 150 ppm and higher blood glucose levels were observed at 150 ppm. No significant changes were found in blood elements or in the battery of tests conducted on urine in the rats that were initially exposed at 14 months of age (Spreafico et al., 1981).

9.2.3. Summary of Acute, Subchronic and Chronic Toxicity.

9.2.3.1. INHALATION EXPOSURE -- Information regarding the acute effects of inhaled EDC in humans is available primarily from cases of occupational exposure (see Section 9.2.1.1). Although the reported cases had both fatal and non-fatal outcomes, many of the reports were foreign and none of the reports provided quantitative exposure data. Further, although EDC was usually reported to be the primary vapor to which the workers were exposed, the preponderance of exposures were to poorly characterized mixtures of EDC and other solvents, or to EDC of unknown purity. Symptoms and signs of acute inhalation exposure were often indicative of CNS and gastrointestinal disturbances, and clinical evidence of liver and kidney dysfunction, as well as irritation of the respiratory tract and eyes, have also been observed. Death was usually ascribed to respiratory and circulatory failure, and autopsies frequently revealed pulmonary edema and congestion, cellular degeneration, necrosis and hemorrhagic lesions of most internal organs (e.g., liver, kidneys, spleen, lungs and respiratory tract, brain, stomach and intestines).

The results of acute experimental studies with three or four subjects suggest that the threshold of light perception (duration of exposure not stated), depth of breathing (1-minute exposure) and vasoconstriction (30-second and 15-minute exposures) increased with exposure to EDC (Borisova, 1957). Spirographic and plethysmographic responses reportedly first differed from baseline values at 1.5 ppm and appeared to be dose-related to 12.4 ppm, the highest level tested; exposure to 1 ppm (the lowest level tested) reportedly had no effect on the physiologic endpoints. Although these Russian experiments appear to indicate a threshold of toxic action, the reliability of the data is uncertain due to the small number of subjects tested and an absence of reported baseline measurements for each subject. Some assurance of data credibility can be gleaned from the fact that the range of concentrations tested (i.e., ≈1-12.4 ppm) represented corroborated subthreshold, threshold and above threshold odor perception concentrates. Borisova (1957) determined the odor perception threshold of EDC to be ≈6 ppm, and this value is consistent with an absolute odor threshold of 6 ppm that was determined by Hellman and Small (1973, 1974) in a Union Carbide study. Further, the sensitivity of the analytic method used by Borisova (nephelometry) appears to be more than adequate to determine EDC at the reported experimental levels. Hellman and Small (1973, 1974) also determined an odor recognition threshold of 40 ppm for EDC.

Acute inhalation studies with a variety of animal species indicate that the effects of single EDC exposures are similar to those in humans. Immediate symptoms of toxicity are related to CNS depression (e.g., narcosis) and delayed histopathologic changes (e.g., congestion and degenerative effects) have been observed primarily in the liver, spleen, kidneys, lungs and adrenals. As detailed in Section 9.2.2.1.3 and Table 9-24, the severity of effects are dependent upon duration and concentration of exposure. For rats exposed for 5-8 hours, it appears that adverse effects are not elicited by exposure at 200 ppm (Spencer et al., 1951); signs of intoxication first appear at 300 ppm (Spencer et al., 1951) and mortality at ≥600 ppm (Heppel et al., 1974; Carpenter, 1949). Concentrations as high as 12,000 ppm were inhaled by rats for 0.1 hours without adverse effects (Spencer et al., 1951).

The dose-response relationships for acute inhalation exposure are not as thoroughly characterized for other species. Corneal opacity was observed in dogs exposed via inhalation to 1000 ppm for 7 hours (Heppel et al., 1944). Signs of intoxication were not present in guinea pigs that were exposed to 1200 ppm EDC for 8 hours (Sayers et al., 1930), but exposure to 1500 ppm for 7 hours produced mortality in mice, guinea pigs and rabbits (Heppel et al., 1945). Histopathological effects (e.g., pulmonary congestion/edema, alterations to kidneys, liver, spleen and adrenals) were generally apparent in rats, mice, guinea pigs and rabbits at concentrations of ≥3000 ppm (Spencer et al., 1951; Heppel et al., 1945; Sayers et al., 1930). Spencer et al. (1930) felt that narcosis that was elicited by concentrations <3000 ppm was attributable to organ injury rather than depression of the CNS.

Limited quantitative data are available, primarily from the foreign literature, regarding the effects of repeated EDC exposure on humans. The studies that are available are deficient because control data are lacking and because durations of exposure and numbers of subjects were poorly characterized. The available data suggest that chronic intermittent exposure in the range of 10-37 ppm may represent a lowest-observed-adverse-effect level (LOAEL) but, as summarized subsequently, the data do not provide a basis for identifying a no-observed-adverse-effect level (NOAEL) or a no-observed-effect-level (NOEL) for humans.

Case reports (Byers, 1943; Rosenbaum, 1947; Guerdjikoff, 1955) and a foreign health survey (Cetnarowicz, 1959) of workers who were exposed repeatedly to 1,2-EDC vapor indicate that typical symptoms and signs of acute poisoning developed with exposure to concentrations in the range of ≈60-200 ppm. In the Cetnarowicz (1959) survey, 16 workers who were exposed to ≈10-200 ppm for 2-8 months were examined; 10 of 10 who were exposed to 60-200 ppm complained of adaptable eye irritation and 6 of the 10 experienced typical symptoms of exposure, but only 1 of 6 exposed to 10-37 ppm were symptomatic. Positive symptoms and signs of exposure, particularly those indicative of mucous membrane irritation, were also observed in 90 of 118 agricultural workers who were concurrently exposed to EDC vapor (≈15-60 ppm) and liquid (prolonged dermal contact) (Brzozowski et al., 1954).

The results of two other foreign health surveys of workers exposed to EDC in the range of the Cetnarowicz (1959) low exposure group (10-37 ppm) support Cetnarowicz's apparent finding that overt symptoms may not be the predominant effect of lower exposures; there appears, instead, to be a prevalence of neurologic and clinical effects. Rosenbaum (1947) examined 100 workers who were exposed to ≤25 ppm for 6 months to 5 years and found disturbances that included "heightened lability" of the autonomic nervous system, increased hidrosis and frequent complaints of fatigue, irritability and sleeplessness, but no hematologic or functional changes of the internal organs. In the study by Kozik (1957), which is particularly notable for its reliable exposure data, workers exposed to time-weighted average concentrations of 10-15 ppm experienced increased morbidity, particularly from gastrointestinal, liver and bile duct disorders. The number of workers surveyed in this study was not clearly stated in the available translation, but it was >83. The occurrence of overt symptoms in these workers was not discussed, but impaired performance on control reaction time tests suggested a possible effect on the nervous system.

Case reports of workers who were repeatedly exposed to unknown concentrations of EDC also suggest that neurologic effects such as nervousness, irritability, tremors and loss of reflexes (McNally and Fostvedt, 1941; Delplace et al., 1962; Suveev and Babichenko, 1969) and complaints of skin and mucous membrane irritation (Suveev and Babichenko, 1969; Rosenbaum, 1947; Guerdjikoff, 1955) are more prevalent in chronically exposed workers than in workers who were acutely exposed.

Studies with several species of animals provide information regarding the threshold region of effects for subchronic and chronic inhalation exposure to EDC. Three studies in which rats, guinea pigs, rabbits, cats and monkeys were exposed to 100 ppm EDC for 7 hours/day, 5 days/week for 4-6 months have shown no treatment-related adverse effects on survival, growth, hematology, clinical chemistry, organ weights or histology (Heppel et al., 1946; Spencer et al., 1951; Hoffman et al., 1971). Adverse effects were also not noted in juvenile mice that were exposed to 100 ppm EDC for 19 exposures (Heppel et al., 1946). The apparent NOAEL of 100 ppm is supported by the results of comprehensive chronic studies with rats in which similar weekly exposures to EDC (7 hours/day, 5 days/week) at concentrations of 5, 10 or 50 ppm for 18-19 months had no significant treatment-related adverse effects on histology (Maltoni et al., 1981) or blood or urine clinical chemistry indices (Spreafico et al., 1981) in rats of either sex; exposure to 150 ppm elicited decreased survival in female rats, but no clear effects on clinical chemistry parameters in either sex. There was an indication of renal and liver damage (increased SGPT, increased serum γ-GT, decreased cholesterol, increased uric acid, increased blood glucose) in mature (i.e., 14-

months-old) rats that were similarly exposed to 50 or 150 ppm EDC for 12 months, but hematologic effects were not found and histological examinations were not conducted.

Subchronic exposure to 200 ppm EDC (7 hours/day, 5 days/week) produced toxic effects in several species, but the severity of effects appeared to vary with investigation. Heppel et al. (1946) observed mortality among rats, mice and guinea pigs exposed to 200 ppm EDC, but not among rabbits or monkeys, and histological lesions were not found in any of these species. Spencer et al. (1951) did not observe mortality in rats or guinea pigs similarly exposed to 200 ppm EDC, but other effects were noted in the guinea pigs (decreased body weight gain and increased liver weight in males, slight hepatic degeneration in males and females). Rabbits and monkeys were not tested by Spencer et al. (1951). An unequivocal frank-effect level (FEL) of 400 ppm is representative for EDC as indicated by production of high mortality and histopathological alterations in the liver and kidney in rats and guinea pigs after a few exposures (Heppel et al., 1946; Spencer et al., 1951). Spencer et al. (1951) reported that exposure to 400 ppm EDC had no effect on rabbits (as reported at 200 ppm), but Heppel et al. (1946) observed some mortality at this level. Exposure to 500 ppm EDC produced high mortality in rats, guinea pigs and rabbits within a few exposures (Hoffman et al., 1971).

9.2.3.2. ORAL EXPOSURE -- Limited data are available on the effects of oral exposure to EDC. Human case reports of accidental or intentional ingestion of EDC indicate that the toxic response to oral exposure is similar to that of inhalation exposure (Section 9.2.1.1.1.1). Ingestion of quantities of EDC estimated to have ranged from 8-200 mℓ have been reported to be lethal (see Table 9-18). This is equivalent to ≈140-3570 mg/kg if it is assumed that an average human weighs 70 kg. Median lethal doses in rats (McCollister et al., 1956; Smyth et al., 1969) and mice (Heppel et al., 1945) have been reported in the range of 700 mg/kg. Higher oral doses (up to 2.5 g/kg) were tolerated by dogs without mortality (Kistler and Luckhardt, 1929). The apparent higher tolerance in dogs and some humans may be related to the ability of these species to vomit. Dose information was not reported in human case reports of non-lethal ingestion of EDC.

Administration of 189 mg/kg/day EDC in the drinking water for 90 days caused a decrease in growth rate in mice, but no significant effects on organ weights, hematology indices, clinical chemistry indices, blood coagulation or immune system function, although a trend towards immunosuppression was noted (Munson et al., 1982). Similar administration of 24 or 3 mg/kg/day EDC in the drinking water for 90 days had no effect on mice.

The only dose-response data that are available for chronic oral exposure to EDC are the results of a 78-week NCI carcinogenesis bioassay with rats and mice (NCI, 1978). Administration of 95 mg/kg/day EDC via gavage (5 days/week) caused early and severe mortality in rats of both sexes, and 47 mg/kg/day caused decreased survival in male rats (after 90 days) and female rats (throughout the experiment). Non-carcinogenic toxic effects appeared to be the cause of the deaths, as indicated by the presence of a variety of lesions including bronchopneumonia and endocardial thrombosis. Body weight depression was not found in any of the treated male or female rats. Treatment-related weight depression and mortality was found in female mice that were similarly exposed to 299 mg/kg/day, but not in females exposed to 149 mg/kg/day or in males exposed to 195 or 97 mg/kg/day. The presence of tumors in the high dose female mice suggested, however, that the deaths may have been tumor-related.

9.3. REPRODUCTIVE AND TERATOGENIC EFFECTS

Murray et al. (1980, unpublished) performed a subchronic inhalation study to determine the effects of ethylene dichloride (1,2-dichloroethane, EDC) on the reproductive ability of rats and effects on their offspring (Murray et al., 1980). The results of this study were reported at the fifth annual Banbury Conference (Rao et al., 1980). Twenty to thirty male and female Sprague-Dawley rats were initally exposed to 25, 75 and 150 ppm EDC (lot no. TAC06228, analyzed as 99.98% pure by Dow Chemical Laboratories) for 60 days (6 hrs/day, 5 days/week for 12 weeks), and then were successively bred to produce two litters, the F_1 and F_{13}. The breeding protocol consisted of caging one male and one female rat for 4 consecutive days, and remating any females that had not mated (no sperm in vaginal smear) with a different male after a 3 day rest period. The results from remated animals were combined with those of the first breeding. The females were exposed to EDC throughout breeding, gestation and lactation (6 hrs/day, 7 day/week) except for day 21 of gestation to day 4 postpartum to allow for delivery and rearing of the young. A second mating, for the production of the F_1 generation took place after the F_{1A} litter was sacrificed (day 21 of birth).

During the seventh week of this study, both control and treated animals suffered from symptoms of sialoacryoadenitis (red crusty material around the eyes and nose and conjunctivitis), which was thought to have resulted from a viral infection. The authors noted that more males than females contracted the disease but suggested that this greater incidence was related to the housing accomodations (males were caged away from females) and not to any greater suceptibility of the males for developing infection after EDC exposure. All animals (both control and experimental) recovered one to two weeks after the onset of the disease with no recurrence for the duration of the study.

Murray et al. (1980) reported that the physical well being of the parental generation was not significantly affected by EDC exposure. However, during the first and second weeks of exposure, the females consumed significantly less food than the controls, although for the rest of the study, there was no alterations in food consumptions. In the males, food consumption was both sporadically increased and decreased throughout the study with a general trend for increased food consumption in males exposed to the highest concentration of EDC (150 ppm) for longer durations of exposure (weeks 15 to 29).

There was a statistical increase in the absolute liver weight at the 150 ppm level, and a statistical linear trend for increased liver weights in adult male rats exposed to EDC (Murray et al., 1980). However, this trend was not observed for liver weights in relation to body weight. All adult males displayed some degree of chronic renal disease, however, the severity of the disease did not appear to be related to treatment. Both control and experimental females displayed signs of renal disease. There was a greater incidence of inflammation and edema of the salivary glands in males exposed to 150 ppm. Three deaths occurred during the course of the study, but these deaths did not appear to be related to EDC exposure.

The fertility and survival index on days 1, 7, 14 or 21, were not statistically different at any dose level. However the greatest pup mortality was observed in groups exposed to 150 ppm between days 14 and 21. The sex ratio, average number of live pups per litter and neonatal body weight were not affected. There were sporadic, statistically significant differences in reproductive indices of treated versus control groups, however, these did not appear to be attributable to EDC exposure. A few neonates exhibited external and internal malformations, however, the incidence of these effects were sporadic and statistically insignificant, reflecting natural variability and not the result of EDC exposure (Murray et al., 1980). Therefore, it was concluded that EDC exposure, under these conditions, did not adversely affect reproduction in rats or the development of their offspring.

Lane, Riddle and Borzelleca (198~~1~~2) evaluated the effects of EDC on the reproductive capability of mice using a multigenerational reproductive protocol modified for screening teratogenic and dominant lethal effects. Animals were exposed to EDC for 35 days, then 10 males and 30 female mice (parental genration F/0) were mated to produce the first set offspring (F/1A). After the F/1A were weaned, the F/0 adults were remated to produce the second set of offspring (F/1B). A parental stock was chosen from the F/1B litter (30 females, 10 males) to produce a second generation of offspring (F/2A). After weaning the F/1B adults were remated to produce offspring (F/2B) for use in teratology and dominant lethal screening tests.

In this study, the EDC (Aldrich Chemical Co. 99% pure) was dissolved in a 1% solution of Emulphor EL-620 (GAF Corp., Linden, NJ) and then further diluted with deionized water to concentrations of 0.03, 0.09, and 0.29 mg/ml or a nominal dose of approximately 5, 15, and 50 mg/kg/day. The test animals were continuously maintained on EDC solutions or control solution (deionized water, or water containing 0.17 mg/ml p-dioxane dissolved in 1.0% Emulphor solution). Fresh drinking solutions were prepared twice weekly and placed in amber glass bottles with cork stoppers and stainless steel drinking tubes.

The authors reported no decreases in fluid consumptions in either the EDC or the solvent control groups.

Lane (198~~1~~2) reported that EDC produced no treatment-related signs of toxicity such as lowered body weights or gross pathological changes in major organs. There were no significant differences in the fertility index or gestation index observed in the F/1A, F/1B or F/2A generations. There were sporadic incidences of increased mortality throughout the generations but these were not dose-related; the reason for the deaths was not apparent at necropsy. There was no difference in the litter sizes at birth, pup body weights, survival of pups at days 4 and 21 of birth. There was a decrease in the survival indices for the F/2A generation as compared to values for the F/1A and F/1B generation but these decreases were not dose related. In the dominant lethal screening tests there were no statistically significant dose-related effects, however both increases as well as decreased were observed in the ratios of dead to live fetuses. In the teratology screening, continous administration of EDC produced no apparent adverse reproductive effects or observable abnormalities. It should be noted that continuous exposure used in this study is not a recommended protocol for evaluating teratogenic effects. In teratology testing, the duration of exposures is usually limited to the period of organogenesis. Also, in the study the F/1C skeletal specimens were lost and, therefore, these effects could not be evaluated.

From this study, (Lane et al., 198~~1~~2) it is not possible to conclusively determine whether EDC has the potential to cause adverse reproductive or teratogenic effects because the doses were not high enough to produce any adverse effects, including maternally toxic effects. However, under the conditions of the experiment, it appears that EDC given in drinking water (nominal doses of 5, 15, 50 mg/kg/day) produced no observable adverse reproductive effects in Swiss ICR mice.

Schlachter et al. (1979) conducted teratology testing in 16 to 30 Sprague-Dawley rats and 19 to 21 New Zealand white rabbits. The animals were exposed by inhalation to either 100 or 300 ppm EDC (Lot Nos. TA0201851L and TA022851L, analyzed as >99.9% pure by the Dow Chemical Laboratories). The rats were exposed 7 hrs/day on days 6 through 15 of gestation. The rabbits were exposed 7 hrs/day on days 6 through 18 of gestation. Two thirds of the maternal rats died when exposed to 300 ppm EDC in contrast to no deaths occurring in the control and 100 ppm groups. In the 300 ppm group, only one rat in six survivors had implantation sites; all of these sites were resorbed. Two additional rats at the 300 ppm level showed early implantation sites when the uterus was stained with sodium sulfide. In the 100 ppm group, threee rats delivered early on day 21; however there were no indication of embryo or fetotoxicity in the offspring. In addition, the rest of the rats at the 100 ppm level delivered normally with no alterations in litter size, number or resorptions of fetal body measurements (crown to rump length).

At the 300 ppm level, one of the six surviving rats had a decrease in mean body weight gain, while in the 100 ppm level, there was an increase in body weights on days 6, 8, 10, 16 and 21 of gestation. At the 300 ppm level, the absolute liver weight was decreased, while the relative liver weight was increased; at the 100 ppm level there was no difference. In the 100 ppm group, there was an increase in water consumption on days 15-17 and 18-20 of gestation, but food consumption was not altered. There was no increase in the occurrence of malformations with only isolated sporadic incidents observed within the range of normal variability.

In this teratology study (Schlachter et al., 1979), four out of twenty-one rabbits in the 100 ppm group, and three out of nineteen rabbits in the 300 ppm group died. Three control rabbits delivered early (days 15, 28, 29 of gestation) as did one animal at the 300 ppm level (day 28 of gestation). Two animals that died at the 100 ppm level, also aborted on days 26 and 28 of gestation. There was no effect on mean litter size, incidence of resorptions or fetal body measurements (crown to rump length) in animals delivering normally. Staining of the uterus revealed only one additional implantation site in control animals. The mean body weights of pregnant animals were generally comparable to that of controls, but there was an increase in mean body weight gains in the 300 ppm group on days 19 through 28 of gestation. A slight but statistically insignificant increase in both absolute and relative liver weights were observed in both the 100 and 300 ppm groups. There was no increase in the incidence of malformations, although sporadic occurances within the range of normal variability were reported. It was concluded from this study that EDC exposure does not produce adverse effects on the developing conceptus.

Several Russian studies by Vozovaya (1971, 1975, 1976, 1977) have reported that EDC produces a number of adverse reproductive outcomes which include: lengthening the total estrus cycle, changes in the duration of various stages of the estrus cycle, increases the number of perinatal embryonic deaths, decreases in the weight of newborn animals, and decreases in the weight gain of offspring after birth. In addition, EDC was reported to concentration in the placenta, amniotic fluid and fetal tissue. However, it is difficult to evaluate or seriously consider these reports since they are presented with insufficient detail for critical scientific review.

Inadequacies in these reports include: lack of original data, various techniques and tests mentioned but results not presented, no information on the source of purity of the chemical, statistical analysis mentioned, but the type of statistical tests not stated.

The above comments apply similarily to the study by another Russian scientist, Urusova (1980), who reported that the EDC accumulated in the milk of nursing mothers. This is obviously an important observation, however, it cannot be accepted as scientific evidence. This report was presented in a subjective, anecdotal manner with many inadequencies in reporting. These inadequencies include: lack of details concerning the numbers of women involved in the study, no data on women's age or physical status, no reporting on the concentrations and duration of EDC exposure after dermal exposure, no information on the repeatability of this finding and no information on number of samples analyzed.

Because of the concern for EDC contamination in mother's milk, Sykes and Klein (1957) conducted a study to determine whether oral administrations of EDC might pass into the milk of cows. Only five cows were used in this study; two cows were exposed to 100 ppm EDC for 22 days; two cows were administered 500 ppm EDC for 10 days followed by 1000 ppm for 12 days; one cow was used as the control. Two different breeds of cows, Holstein and Jersey cows were used but it was not stated which cows received which dose. Seven milk samples collected over a three week period containing no more than 0.4 ppm EDC, however, the authors stated that this amount was too low for accurate detection by the Volhard titration method used in this study. The samples collected from cows ingesting EDC had consistently higher concentration of EDC than the controls, but because of the small sample size, and the lack of sophisticated analytical procedures, it is not possible to make firm conclusions as to the amount of EDC entering the milk supply. More importantly, this study was not designed to evaluate the possible health consequences of EDC injested in the milk of nursing offspring. However, recent pharmacokinetic studies do indicate that EDC has a tendency to accumulate in fatty tissues (Spreafico et al., 1980) although the reproductive health effects of EDC in breast milk have not been evaluated.

9.3.1. Summary. The available scientific information on the potential of ethylene dichloride (EDC) to adversely affect reproductive or developmental processes includes a teratoglogy test conducted in rats and rabbits (Schlachter et al., 1980), a single-generation reproductive test conducted in rats (Murray et al., 1980), a multigenerational reproductive test conducted in mice (Lane et al., 198~~1~~2), several reports by Russian scientists describing a number of adverse reproductive effects observed in laboratory animals and man (Vozovaya 1971, 1975, 1976, and Urusova 1953), and an investigation measuring the amount of EDC found in the milk of cows after ingesting EDC (Sykes and Klein, 1953).

The results of reproductive and teratogenicity testing (Murray et al., 1980, Schlachter et al., 1979, and Lane et al., 198~~1~~2) indicate that EDC has little potential for producing adverse reproductive affects or adversely affecting the developing conceptus, except when the mother is exposed to doses high enough to produce maternal toxicity. The Russian studies describing a variety of adverse reproductive effects associated with EDC exposure do not provide conclusive scientific evidence because the studies were inadequately performed or reported. The study of EDC in the milk of cows is inadequate sophisticated analytical procedures, it is not possible to make firm conclusions as to the amount of EDC entering the milk supply. More importantly, this study was not designed to evaluate the possible health consequences of EDC injested in the milk of nursing offspring. However, recent pharmacokinetic studies do indicate that EDC has a tendency to accumulate in fatty tissues (Spreafico et al., 1980) although the reproductive health effects of EDC in breast milk have not been evaluated.

9.3.1. Summary. The available scientific information on the potential of ethylene dichloride (EDC) to adversely affect reproductive or developmental processes includes a teratoglogy test conducted in rats and rabbits (Schlachter et al., 1980), a single-generation reproductive test conducted in rats (Murray et al., 1980), a multigenerational reproductive test conducted in mice (Lane et al., 198~~1~~2), several reports by Russian scientists describing a number of adverse reproductive effects observed in laboratory animals and man (Vozovaya 1971, 1975, 1976, and Urusova 1953), and an investigation measuring the amount of EDC found in the milk of cows after ingesting EDC (Sykes and Klein, 1953).

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9.4. MUTAGENICITY

Ethylene dichloride (EDC) has been tested for mutagenic activity in bacteria, plants, Drosophila, mammalian cells in vitro, and rodents. These studies are discussed below and are summarized in Tables 9-27 to 9-32. The reader may also refer to published reviews of the mutagenic potential of EDC (e.g., Fishbein 1976 and 1979, Fabricant and Chalmers 1980, Rannug 1980, or Simmon 1980).

GENE MUTATION STUDIES

Bacterial Test Systems

Many investigators have studied the ability of EDC to cause gene mutations in bacteria (Table 9-27). Most reported marginal positive responses without metabolic activation and stronger positive responses with exogenous hepatic metabolic activation, indicating that EDC is weakly mutagenic by itself but that metabolites, such as S-(2-chloroethyl)-L-cysteine, are more potent mutagens.

Ethylene dichloride has been reported positive in four Salmonella/microsome plate incorporation assays (McCann et al. 1975, Rannug 1976, Rannug and Ramel 1977, and Rannug et al. 1978), in assays testing the mutagenicity of bile obtained from EDC-perfused rat livers or livers from EDC-treated mice (Rannug and Beije 1979) and in two Salmonella spot tests. In one of the Salmonella spot tests, (Brem et al. 1974) an analysis of duplicate experiments carried out on at least three different occasions revealed a twofold increase in revertant counts for strains TA1530 and TA1535 (mean values of 50 and 54 revertants on treated plates versus 23 and 26 in control plates for TA1530 and TA1535, respectively). No difference in revertant counts was noted for strain TA1538. This response is consistent with that expected for an alkylating agent. The authors stated that plate incorporation tests could not be performed because of the volatility of the test agent. Positive and negative control tests were conducted for these experi-

TABLE 9-27

Summary of Mutagenicity Testing of EDC: Gene Mutations in Bacteria

Reference	Test System	Strains	Activation System	Chemical Information	Results	Comments
Brem et al. 1974	*Salmonella* (spot test)	TA1535 TA1535 TA1538	None	10 µmoles on filter disk Source: Not given Purity: Not given	Weak positive	1. Could not perform plate incorporation tests because of volatility.

	Salmonella revertants		
	TA1530	TA1535	TA1538
EDC	50	54	19
Water	23	26	19
Chloramphenicol	20	31	14

TABLE 9-27 (cont.)

Reference	Test System	Strains	Dose µl/Plate				Comments
			-S9		+S9		
			0	100	0	100	
Principe et at . 1981	*Salmonella*/ mammalian microsome assay (spot test)	TA1535	39	46	33	103*	1. Positive controls indicated system working properly. 2. Positive results in *Salmonella* in spot test with TA1535. 3. No precautions taken to prevent excessive evaporation of EDC and insure adequate exposure. 4. Toxicity results indicate exposure was minimal.
		TA1537	17	8	10	8	
		TA1538	19	12	21	27	
		TA98	82	83	77	84	
		TA100	188	188	171	169	
		*P<0.01					
	S. coelicolor forward mutation assay to Str^r		Dose µl/plate		Survival %	Str^r/plate	
			0		100	2.5 ± 0.6	
			2		100	0.2 ± 0.2	
			10		100	0.7 ± 0.4	
			20		100	0.7 ± 0.4	
			100		100	1.0 ± 0.8	
						8-AG/Plate	
	A. nidulans forward mutation to $8\text{-}AG^r$		0		100	2.5 ± 0.9	
			250		100	2.0 ± 1.1	
			500		42	1.0 ± 0.7	

TABLE 9-27 (cont.)

Reference	Test System	Strains	Activation System	Chemical Information	Results	Comments
McCann et al. 1975	Salmonella/ microsome assay (plate test)	TA100	PCB-induced rat liver S9 mix	Concentration Tested: 1.3×10^3 µg/plate (13 µmoles) Source: Aldrich Chemical Co. Purity: Not given, but stated to be highest purity.	Negative or at best only marginal positive response. Induced 25 colonies plate above background. (0.19 revertants/µmol) in TA100	1. Non-mutagenic or extremely weak mutagen in this study. Reproducible dose-response curves not obtained. 2. Metabolic activation did not increase positive response. 3. Chloroethanol and chloroacetaldehyde (two putative intermediates in the metabolism of EDC in mammals) tested positive (i.e., 0.06 and 746 revertants/µmol, respectively).
Rannug 1976	Salmonella/ microsome assay (plate test)	TA1535	Liver fractions from Sprague-Dawley or R strain Wistar rats induced with phenobarbital with and without NADPH-generating system and with and without glutathione S-transferases A, B and C.	Concentration tested: Up to 60 µmol/plate Source: BDH Chemicals, Ltd. Purity: Not given but reported to be checked by glass capillary column chromatography using a flame ionization detector	Marginally positive without activation (twofold increases); positive response with activation (tenfold increases). Spontaneous background 8-14 revertants/plate.	1. EDC activated by the liver cytosol fraction, Mixed-function oxygenases not involved. 2. NADPH-independent GSH S-transferase dependent activation. 3. Strain differences noted in ability to metabolize EDC. 4. Thought that mugatenicity of EDC after activation caused by formation of highly reactive half sulfur mustard, S-(2-chloroethyl)-L-cysteine.

TABLE 9-27 (cont.)

Reference	Test System	Strains	Activation System	Chemical Information	Results	Comments
Rannug and Ramel 1977	*Salmonella*/ microsome assay (plate test)	TA1535	S9 mix from livers of uninduced male N strain Wistar rats plus NADPH generating system	Concentration tested: Up to 45 µmol/plate Source: BDH Chemicals, Ltd. Purity: Not given	Positive response (two fold increase without activation; nearly tenfold increase with activation.) Negative controls yielded roughly 15 revertants/plates.	1. Compared mutagenicity of EDC tar with EDC. The level of EDC present at the highest dose tested for EDC tar would only exert a weak mutagenic effect, yet a strong response was observed. 2. Activation of EDC tar dependent on NADPH. EDC activation independent of NADPH.
Rannug et al. 1978	*Salmonella*/ microsome assay (plate test)	TA1535	Rat liver microsome system with and without NADP	Concentration tested: 45 µmol/plate Source: EDC given BDH Chemicals, Ltd. Purity: Not given for EDC, but checked using glass capillary chromatography using a flame ionization detector.	Marginal positive response without activation (twofold increase 24.8 ± 3.06 at 45 µmol v. 13.0 ± 1.76 control); positive response with activation (10-fold increase) independent of presence of NADP.	1. EDC major component of EDC tar. Mutagenicicity of tar increased with metabolic activation only with addition of NADP. 2. Mutagenicity of EDC tar not solely due to EDC.

TABLE 9-27 (cont.)

Reference	Test System	Strains	Activation System	Chemical Information	Results	Comments
Rannug and Beije 1979	Salmonella/ isolated perfused rat liver	TA1530 TA1535	Isolated perfused liver from male R strain Wistar rats.	Concentration tested: 0.1 mℓ (1.3 mMoles) for up to 4 hours.	Positive. Highest response 15-60 minutes after addition of EDC (45-60 revertants compared to 7-10 in controls).	1. Positive responses consistent with conjugation of EDC with glutathione.
	Salmonella/ (plate test)	TA1535	Bile from male CBA mice.	80 mg/kg EDC i.p.; removal of liver and collection of bile 30 and 60 minutes later.	Positive. Greater than twofold increases with bile from liver removed 30 minutes after addition of EDC (28.8 ± 27 revertants compared to 11.3 ± 1.1).	
King et al. 1979	Salmonella/ microsome assay (plate test)	TA1535 TA100 TA1537 TA1538 TA98	PCB-induced rat liver S9	Concentration tested: 36 µmoles/plate	Negative	1. Standard plate incorporation test was conducted. No precautions were taken to prevent excessive evaporation of EDC.
	E. coli K 12/ 343/113 (suspension test and intrasanguineous host-mediated assay).			10 mM (suspension assay)	Negative	
				2 mM/kg i.p. injection female NMRI mice	Negative	
				Source: Merck Co. Darmstadt, FRG		
				Purity: Not given. Stated that samples had correct melting point and elemental analysis.		

TABLE 9-27 (cont.)

Reference	Test System	Strains	Activation System	Chemical Information	Results	Comments
Nestman et al. 1980	Salmonella/ microsome assay (plate test and and desiccator exposure).	TA1535 TA100 TA1537 TA1538 TA98	PCB-induced rat liver S9 mix.	Concentration tested: Up to 9 mg/plate (91 µmoles) in desiccators. 10 mg/plate in plate tests. Source: Chem Service Purity: Not given Solvent: DMSO	Negative in standard test. Positive in desiccator testing in strain TA1535.	1. Stated that maximum yield with TA100 is 20 revertants above background (i.e., negative). For TA1535 a doubling of mutant colonies observed. No other data presented. 2. Cannot adequately evaluate results.
Stolzenberg and Hine, 1980	Salmonella/ microsome assay (plate test)	TA100	PCB-induced rat liver S9 mix (2 mg protein/0.5 mℓ).	Concentration tested: Up to 10 µmoles/plate Source: Aldrich Chemical Co. Purity: 99% pure	Negative	1. All compounds tested in triplicate with and without S9 mix. 2. Experimental values minus background revertants.

	Revertants	
µmoles/plate	-S9	+S9
10^{-1}	0	0
1	0	0
10	15 Toxic	No growth

TABLE 9-27 (cont.)

Reference	Test System	Strains	Activation System	Chemical Information	Results	Comments
Barber et al. 1981	Salmonella/ microsome assay (vapor exposure)	TA1535 TA100 TA1538 TA98	PCB-induced rat liver S9 mix.	Concentration tested: Up to 231.8 µmole/plate as determined by GLC analysis of distilled water samples. Source: Eastman Kodak Co. Purity: 99.98%	Negative in standard plate test. Positive in desiccator testing in strains TA1535 and TA100.	1. Bacteria exposed in gas tight exposure chambers. 2. Plastic plates found to absorb dibromomethane in parallel experiment. Thus, glass plates used for all other testing. 3. Weak positive result. 0.002 revertants/nmole TA1535 with or without activation. 0.001 revertants/nmol TA100 with or without activation. 4. Revertants selected from each experiment and tested to ensure that they were actually his^+.

ments and indicated the systems were working properly. Principe et al. (1981) conducted a spot test using strains TA1535, TA1537, TA1538, TA98, and TA100. A positive response was observed for TA1535 when a triangular shaped paper disc soaked with 100 μℓ EDC was placed on the agar in the presence of S9 from Aroclor 1254-induced rat liver (i.e., 103 revertants on the treated plate vs. 33 revertants for the negative control). Negative responses were obtained with the other strains. A negative response was also obtained in plate incorporation tests conducted with TA100 and TA1535 at doses up to 100 μℓ/plate. A standard assay was conducted; no precautions were taken to prevent excessive evaporation of the EDC. Similarly in forward mutation tests conducted with *Streptomyces coelicolor* and *Aspergillus nidulans* negative responses were obtained at doses up to 100 and 500 μℓ/plate in plate incorporation and spot tests. There was a 100% survival in the test conducted with *S. coelicolor* and a 60% reduction in cell survival at the highest dose with *A. nidulans*. Thus, these tests are judged to provide less than adequate conditions for assessing the mutagenicity of EDC because insufficient exposure to the test organisms may have occurred.

McCann et al. (1975) exposed *Salmonella* strains TA1525, TA100, and TA98 to EDC (Aldrich, stated to be highest purity available) concentrations as high as 13 mg/plate (131 μmoles/plate). A weak positive response was observed in TA100 (0.19 revertants/μmol). However, reproducible dose-related response curves were not obtained. The presence of an exogenous S9 mix metabolic activation system (from rat livers induced with either phenobarbital or Aroclor 1254) did not increase the weak positive response. Chloroacetic acid, which is a known mammalian metabolite of EDC, and the putative intermediates (i.e., chloroethanol and chloroacetaldehyde see sections 9.1.3.3A), were also tested for their mutagenic potential. Chloroacetic acid was negative, but chloroethanol yielded a weak positive and chloroacetaldehyde a strong positive result (0.06 and 746 rever tants/μmol, respectively, in TA100). The authors speculated that the weak mutagenic response of EDC may be due to relatively inefficient conversion of chloroethanol to chloroacetaldehyde in the _in vitro_ system.

Two reports (Rannug 1976; and Rannug and Ramel 1977) compared the mutagenicity of EDC with that of EDC tar, a complex mixture formed during the manufacture of vinyl chloride from either acetylene, ethylene, or a mixture of the two. The mixture is called EDC tar because ethylene dichloride is a major component comprising about 30% of the mass. The sample of EDC tested in these studies was from British Drug House (BDH) Chemicals, Ltd. (purity not given). _Salmonella_ tester strain TA1535 was dosed up to 45 μmoles/plate in the presence or absence of an exogenous metabolic activation system (from livers of male strain R Wistar rats) with and without NADP. Weak positive (twofold) increases in revertant frequencies over background (13.0 ± 1.76) were observed in the plates receiving the highest dose (24.8 ± 3.06) in tests conducted without metabolic activation. However, with activation, a strong positive response was observed. The revertant count was elevated tenfold over the spontaneous level (132.8 ± 8.35 v. 15.5 ± 1.21). The response to EDC was independent of the presence of NADP; in constrast, the mutagenicity of EDC tars was increased with metabolic activation only in the presence of NADP. It was concluded that the mutagenicity of EDC tar cannot be ascribed primarily to EDC, because EDC and EDC tar have different requirements for metabolic activation. In addition, the concentration of EDC present in EDC tar at the highest dose tested would yield only a weak positive response if tested alone, while in fact a strong response was observed for the EDC tar.

Following these observations, Rannug et al. (1978) tested _Salmonella_ strain TA1535 with EDC (BDH Chemicals Ltd.; although the purity was not reported, the material was checked by glass capillary chromatography using a flame ionization detector) at doses up to 60 μmoles/plate. Tests were conducted with and without an exogenous rat liver metabolic activation system. The components of the activation system were varied in order to study the mechanism of activation of EDC. Phenobarbital-induced liver fractions from Sprague-Dawley or R strain Wistar rats were prepared with and without an NADPH-generating system and with and without glutathione transferases A, B, and C. It was observed that EDC is activated by the cytosol fraction of liver homogenates; thus, mixed-function oxygenases are not involved. The activation was NADPH-independent but required glutathione (GSH) A or C S-transferase enzyme activity. The extent of activation was found to be dependent on the rat strain used (liver fractions from R strain rats were more effective than those from Sprague-Dawley rats) and the handling of the extract (e.g., storage on ice or freezing reduced the effectiveness of the activation system). The report by McCann et al. (1975) (described earlier in this section) that EDC was not metabolized to a mutagenic intermediate may be due to differences in the exogenous activation system used (S9 mix rather than cytosol fraction) in the two studies. Rannug et al. (1978) hypothesize that the mutagenicity of EDC after metabolic activation is caused by the formation of a highly reactive half sulfur mustard, S-(2-chloroethyl)-L-cysteine (see section 9.1.3.3.B). This compound (>99% purity) was found to be more strongly mutagenic in TA1535 than is EDC. AT 0.2 μmoles/plate, 12.8 ± 1.5 and 176.8 ± 11.1 revertants were observed per plate after treatment with EDC and S(2-chloroethyl)-L-cysteine, respectively. At 5.0 μmoles/plate the observed numbers of revertants per plate were 13.0 ± 1.1 and 1954 (only one plate tested), respectively. Thus, S-(2-chloroethyl)-L-cysteine gives a strong direct mutagenic effect at low doses where no effect can be seen for EDC.

In intact mammals most GSH conjugates are normally excreted in bile. Rannug and Bieje (1979) reasoned that if EDC were metabolically activated by conjugation with glutathione to form a half sulfur mustard, mutagenic products in the bile would be produced in EDC-treated mammals or perfused livers. To test this hypothesis, an EDC concentration of 0.1 mℓ (1.3 mmoles) were perfused through R strain Wistar rat livers for up to 4 hours. Bile was collected right after addition of EDC and at 15 and 30 minutes, as well as 1, 1.5, 1.75, 2, 3, and 4 hours later. The bile was then added directly to top agar or diluted about 5 to 10 times in sterile water and added to top agar containing Salmonella strain TA1535 for plate incorporation tests. Positive responses were obtained. The greatest response (45-60 revertants per plate, compared to 7-10 in negative controls) was reached about 15 minutes to 1 hour after addition of EDC. In a second experiment, 80 mg/kg EDC was given to male CBA mice intraperitoneally. The animals were sacrificed, their livers removed, and bile collected 30 and 60 minutes later for mutagenicity testing with TA1535 in plate incorporation tests. An increase in revertants (greater than twofold) was observed for bile collected 30 minutes after treatment compared to bile from negative control animals (28.8 ± 27 revertants and 11.3 ± 1.1 revertants, respectively). The positive responses obtained with bile from the perfused rat livers and intact mouse livers are consistent with the hypothesis that EDC is activated by conjugation with glutathione.

Four studies have been reported in which EDC was found to be negative in the standard Salmonella/microsome assay plate incorporation tests (King et al. 1979, Nestmann et al. 1980, Stolzenberg and Hine 1980, and Barber et al. 1981). The maximum doses employed in the first three studies were 36 μmoles/plate, 91 μmoles/plate, and 10 μmoles/plate, respectively; the fourth study did not report the doses used. The doses reported in these studies therefore encompass a range at which positive responses have been reported in other studies. Except for the report by Stolzenberg and Hine (1980), the negative Salmonella plate incorporation studies were conducted with appropriate positive controls. Each test was conducted with and without PCB-induced rat liver S9 mix. It should be pointed out, however, that the positive controls, which require activation, were not structually similar to EDC. Therefore, these positive controls may not be able to determine the effectiveness of the components in the S9 mix necessary for EDC activation. King et al. (1979) also reported negative responses when E. coli K12/343/113 was tested in either a liquid suspension test or an intrasanguineous host-mediated assay.

Two of the negative studies (i.e., Nestmann et al. 1980 and Barber et al. 1981) reported that although EDC did not induce mutations in standard plate incorporation tests, positive responses were obtained when the studies were conducted in air tight exposure chambers. Nestmann et al. (1980) exposed Salmonella strains TA1535 and TA100 to doses from 3 to 9 mg/plate (30 to 91 μmoles/plate) in desiccators. It was reported that this treatment yielded positive results, at least for TA1535 in which there was a doubling in the number of mutant colonies over the control. It was stated that concentrations were tested up to levels where cell-killing was observed, but no data are given and insufficient detail is provided to allow the results be adequately evaluated.

Barber et al. (1981) exposed Salmonella tester strains TA1535, TA98, and TA100 to four levels of EDC vapors (Eastman Kodak Co., 99.98% pure) in a 3.4 liter airtight exposure chamber. These exposures resulted in estimated plate concentrations ranging from 31.8 to 231.8 μmoles/plate as determined by gas liquid chromatography analysis of distilled water samples placed in the exposure chamber. Linear, dose-related increases in revertant counts were observed for TA1535 and TA100. The mutagenicity of EDC in these two strains was 0.002 and 0.001 revertants/nmole, respectively. No difference in revertant counts or potency of EDC was noted in comparisons of tests done with and without metabolic activation. The positive results were obtained by Nestmann et al. (1980) and Barber et al. (1981) only when tests were conducted in airtight exposure chambers. This suggests that standard mutagenicity testing of EDC (bp 83-84°) may not provide an adequate assessment of its mutagenic potential due to excessive evaporation.

In summary, the positive responses obtained without metabolic activation indicate that EDC is a weak direct-acting mutagen in bacteria. The positive responses obtained with metabolic activation indicate that one or more of its metabolites are more potent mutagens. The negative findings reported in bacterial tests are not considered to contradict the reported positive results, because the negative results may have been due to excessive evaporation of EDC or to inadequacy of the S9 activation system.

Eucaryotic Test Systems

In addition to causing gene mutations in bacteria, EDC also has been shown to cause gene mutations in eukaryotes.

Higher Plants --

Two reports were evaluated concerning the ability of EDC to induce mutations in higher plants (Table 9-28). Ehrenberg et al. (1974) treated barley seeds (variety Bonus) with 30.3 mmoles EDC (Merck, purity not given) for 24 hours and scored for sterile spikelets at maturity or chlorophyll mutations in about 600 spike progenies in the subsequent generation. The dose level tested corresponds to the LD_{50}. EDC treated kernels had an increased incidence of chlorophyll mutations (6.8%) compared to untreated controls (0.06%).

Kirichek (1974) exposed eight varieties of pea seeds (100 each) to gaseous EDC (purity and concentration not given) for 4 hours. The germination of treated seeds differed with the variety tested but was reduced (15-50% germination) compared to negative control seeds exposed to water vapor for 4 hours (100%

TABLE 9-28

Summary of Mutagenicity Testing of EDC: Higher Plants

Reference	Test System	Chemical Information	Results	Comments
Ehrenberg et al. 1974	Segregating chlorophyll (gene) mutations in barley.	Concentration tested: 200 seeds treated with 30.3 mmoles/24 hours (LD_{50}) in a closed vessel.	Positive response. (6-8% mutants from treated progeny vs. 0.06% mutants from control progeny). Source: Merck Co. Purity: Not given	1. About 600 spike progeny were tested.
Kirichek, 1974	Visible mutations in peas, 8 varieties	Concentration tested: EDC (concentration not reported) or water (negative controls) vapors for 4 hours. Source: Not reported Purity: Not reported	Reported postive. 5.42-28.13% of seeds reported to be mutated.	1. English translation of Russian article. 2. Germination of the treated seed varied with the variety tested from 15% to 58% compared to 100% germination of the control seeds. 3. Control mutation frequency not given. 4. Putative mutations not characterized. 5. Not possible to adequately evaluate results.

germination). From 5.4% to 28.13% of the seeds were reported to be mutated. It is reported that two times as many morphological mutants were induced as chlorophyll mutations. The author considered this a positive response, but the mutation frequency for negative controls was not given. This limitation of the report plus a lack of information concerning the characterization of the putative mutations precludes an adequate evaluation of the results.

Insects --

Four studies were evaluated concerning the ability of EDC to cause mutations in *Drosophila melanogaster* (Table 9-29). These studies demonstrated the ability of EDC to cause sex-linked recessive lethal mutations (Shakarnis 1969, Shakarnis 1970, and King et al. 1979). The fourth study demonstrated the induction of somatic cell mutations by EDC (Nylander et al. 1979).

Shakarnis (1969, 1970) performed two experiments to assess the ability of EDC (purity not given) to cause sex-linked recessive lethal mutations in *Drosophila*. In the first study (Shakarnis 1969), adult females from a radiosensitive strain (Canton S) were exposed to 0.07% EDC gas for 4 or 8 hours at 24°-25°C. Immediately after treatment the females were mated to Muller-5 or *In* w^a *B* males. In fertility of treated females was reduced 47% by the 4 h treatment and 91% by the 8 h treatment. The F_2 progeny were scored for lethality (measured as the absence of M5 or *In* w^a *B* males). A statistically significant ($P<0.05$) time-related increase in the incidence of sex-linked recessive lethals was observed. The frequencies of lethals were 0.3% (negative controls), 3.2% (4 h treatment) and 5.9% (8 h treatment). In his second study, Shakarnis (1970) exposed females from a radiostable strain (D-32) of *Drosophila melanogaster* to 0.07% EDC vapors (source and purity not reported) for 4 or 6 hours. Immediately after treatment they were mated to Muller 5 males and the F_2 progeny scored for sex-linked recessive lethals. The 4 h treatment did not significantly reduce fertility but

TABLE 9-29

Summary of Mutagenicity Testing of EDC: Gene Mutation Tests in Insects

Reference	Test System	Chemical Information	Results	Comments
Shakarnis, 1969	Drosophila melanogaster sex-linked recessive lethal test.	Concentration tested: virgin 3-day-old Canton S females exposed to 0.07% EDC gas for 4 or 8 hours at 24-25°C. Source: Not given Purity: Not given	Postive response	1. Muller-5 or In w^a B males. 2. Fertility of treated females reduced significantly (47% after 4 hour treatment and 91% after 8 hour treatment). 3. Canton S strain reported to be sensitive.

Duration of Treatment (h) with 0.07% EDC	Number of Chromosomes Scored	Lethal Mutations No.	Lethal Mutations %
Control	4910	15	0.30
4	2081	67	3.22
8	4750	281	5.91 $p<0.05$

TABLE 9-29 (cont.)

Reference	Test System	Chemical Information	Results	Comments
Shakarnis, 1970	Drosophilia melanogaster sex-linked recessive lethal test.	Concentration tested: virgin 3-day-old radiostable D-32 strain females exposed to 0.07% EDC gas for 4 or 6 hours at 24-25°C. Source: Not given Purity: Not given	Positive response	1. Muller-5 males. 2. Experiment conducted twice for 4 hour exposure and three times for 6 hour exposure. 3. 4 hour treatment did not significantly reduce fertility but 6 hour treatment reduced it by 50%.

Duration of Treatment (h) with 0.07% EDC	Number of Chromosomes Scored	Lethal Mutations No.	Lethal Mutations %
Control	1904	1	0.05
4	2205	46	2.00
6	2362	78	3.30 (P<0.05)

TABLE 9-29 (cont.)

Reference	Test System	Chemical Information	Results	Comments
King et al. 1979	Drosophila melanogaster sex-linked recessive lethal test.	Concentration tested: 50 mM solution of EDC in 5% sucrose fed to 1- to 2-day-old Berlin K males for 3 days (Near LD_{50}). Source: Merck Co. Darmstadt, FRG Purity: Not given but stated to have correct melting point and elemental analysis.	Positive response	1. Basc females. 2. Lethal frequency increased for all broods. Greatest effect in brood II, which corresponds to the spermatid stage of spermatogenesis.

Conc. (mM)	Brood	Days after Treatment	Number of Chromosomes Scored	Lethal Mutations No.	Lethal Mutations %	Lethal Mutations P
0	I-III	0-9	22,048	47	0.21	
50	I	0-3	1,185	6	0.51	
	II	4-6	1,179	41	3.48	<0.01
	III	7-9	156	2	1.28	
	I-III	0-9	2,520	49	1.94	<0.01

TABLE 9-29 (cont.)

Reference	Test System	Chemical Information	Results	Comments
Nylander et al. 1978	*Drosophila melanogaster* somatic cell mutations *so* *z* *w*$^{+}$ and *z* DPW^{+01e19} stocks.	Concentration tested: 0.1% and 0.5% EDC in food at 25°C and 75% humidity during larval development. Source: Fisher Scientific Co. Purity: Not given	Positive response	1. Mutations at *z* locus scored in flies of stable and unstable genotype. Both have same phenotype. Instability thought to be caused by transposable genetic element. 2. Survival of treated flies reduced significantly in both genetically stable (34% reduction for 0.1% and 77% reduction for 0.5% dose) and genetically unstable stocks (86% reduction for 0.5% dose).

Treatment	Number Males Scored	Number with Sectors	%	t Value Differences Within Genotypes	t Value Differences Between Genotypes
Control					
Stable	4441	2	0.045	---	
Unstable	5363	4	0.075	---	0.60
0.01%					
Stable	6260	263	4.20	18.74[a]	
Unstable	2899	274	9.28	24.31[a]	9.16[a]
0.05%					
Stable	610	44	7.21	11.46[a]	
Unstable	201	50	24.88	13.12[a]	5.66[a]

unstable stock at 0.5% EDC). Statistically significant increases in somatic cell mutations occurring in both stocks were observed at both the low and high doses ($P<0.001$).

The positive responses in Drosophila indicate that EDC is capable of causing both somatic cell and heritable germinal mutations in a multicellular eukaryote.

Mammalian Cells In Culture --

Tan and Hsie (1981) found that EDC (Matheson, Coleman and Bell, purity not given) caused a dose-related increase in HGPRT mutations in cultured Chinese hamster ovary (CHO) cells (Table 9-30). CHO-K_1-BH_4 cells were exposed in suspension culture for a period of 5 hours to EDC concentrations ranging up to 3mM (30% survival) in tests with exogenous rat liver S9 mix for metabolic activation and concentrations ranging up to 50mM (50% survival) in tests conducted without metabolic activation. Weak positive responses were observed both in tests with (5 mutants/10^6 cells/mM) and without (1 mutant/10^6 cells/mM) metabolic activation ($P<0.01$). EDC was detected as a direct-acting mutagen only at high doses, but the induced mutation frequency was increased about tenfold over control values. Only about a fourfold additional increase in mutagenicity was noted with metabolic activation but excessive toxicity precluded testing at concentrations greater than 3mM (i.e., S9 mix increased mutagenic activity by approximately fourfold and cytotoxic activity from 5 to 25-fold). The metabolic activation system was only effective in the presence of NADP. This contrasts with Rannug (1976) who found metabolic activation of EDC to be NADP-independent.

The consistency of positive results obtained in higher plants, Drosophila, and cultured mammalian cells demonstrates that EDC causes gene mutations in higher eukaryotes.

the 6 h treatment reduced it by 50%. As in the first study, a statistically significant ($P<0.05$) time-related increase in sex-linked recessive lethals was observed. A frequency of 0.05% lethals was observed in the negative controls, and frequencies of 2.00% and 3.30% lethals were observed in offspring from the 4 h and 6 h treatments, respectively.

King et al. (1979) also studied the ability of EDC to cause sex-linked recessive lethals in *Drosophila*. One to two day old Berlin K males were fed a 50 mM solution of EDC (Merck and Co., purity not given but correct melting point (sic) and elemental analysis reported) in 5% sucrose for 3 days. This dose approximated the LD_{50}. The males were immediately mated to virgin *Basc* females every 3 days for a total of 9 days to determine if EDC preferentially damaged particular stages in spermatogenesis. Progeny of the F_2 generation were scored for lethality. The lethal frequency was found to be elevated for all three broods (0.51%, 3.48%, and 1.28%, respectively, for broods I, II, and III) compared to the negative controls (0.21%). The highest lethal frequency (3.48%) was found in brood II ($P<0.01$), which corresponds primarily to the spermatid stage of spermatogenesis.

Nylander et al. (1979) raised flies on food containing 0.1% and 0.5% EDC (Fisher Scientific Co., purity not given) during larval development and scored F_1 progeny for the induction of somatic cell sex-linked mutations in the eye. A genetically unstable stock ($\underline{sc}\ \underline{z}\ \underline{w}^{+}$) and a genetically stable stock ($\underline{z}$ Dp w^{+61e19}) both having the same phenotype were used in these studies and mated to attached X females. Mutations result in the expression of normal (dark red) eye pigment in adult treated males. The genetic instability of $\underline{sc}\ \underline{z}\ \underline{w}^{+}$ is caused by the insertion of a transposable genetic element. The survival of flies raised on the EDC-treated food was significantly reduced compared to the negative control values (e.g., 77% reduction for the stable stock and 86% reduction of the

TABLE 9-30

Summary of Mutagenicity Testing of EDC: Mammalian Cells in Culture

Reference	Test System	Chemical Information	Results	Comments
Tan and Hsie, 1981	Chinese hamster ovary cell HGPRT gene mutation assay.	Concentration tested: Up to 3 mM in tests with rat liver S9 mix and up to 50 mM in tests without metabolic activation. LD_{50} is 1 mM with activation and 6 mM without activation.	Positive response 60 v. 3 mutants/10^6 clonable cells for 50 and 0 mM EDC without activation. 28 v. 3 mutants/10^6 clonable cells for 1.5 and 0 mM EDC with activation.	1. Mutagenic activity of EDC without and with metabolic activation calculated to be 1 and 5 mutants/10^6 cells/millimole, respectively. 2. S9 mix increases mutagenicity by about fourfold and cytotoxicity 5- to 25-fold. 3. NADP required in S9 mix for metabolic activation.

CHROMOSOME ABERRATION STUDIES

Five studies were evaluated regarding the ability of EDC to cause chromosome aberrations (Table 9-31). One was an abstract of testing EDC for its ability to cause chromosome breakage in Allium root tips and cultured human lymphocytes (Kristoffersson 1974). Two were Drosophila melanogaster X chromosome nondisjunction tests (Shakarnis 1969 and 1970), and two were micronucleus tests (King et al. 1979 and Jenssen and Ramel 1980).

In the report by Kristoffersson (1974) EDC (source, purity, and concentration not given) was reported to cause C-mitoses in Allium root tip cells but not to cause chromosome breaks in Allium root tip cells, human lymphocytes or to induce prophage from E. coli K 39 (λ). Because the report was an abstract, insufficient information was available to substantiate the reported results. However, the induction of C-mitoses in Allium root tip cells suggests that EDC can interfere with the mitotic spindle apparatus.

Data consistent with this possibility are found in studies by Shakarnis (1969 and 1970) using Drosophila melanogaster. Females were exposed to 0.07% EDC vapors (source and purity not given). In the first study (1969) a statistically significant ($P<0.05$) increase in exceptional F_1 progeny, indicative of meiotic nondisjunction, was seen after a 4 h treatment (0.03% exceptional females) and 8 h treatment (0.18% exceptional females and 0.09% exceptional males) compared to the negative control value (0%; 0/11575 progeny). In the second study, the incidence of exceptional progeny was elevated in the treated groups but not significantly so. However, in this study 38,437 fewer progeny of the 4 h treatment group were scored for exceptional progeny than in the first study. Furthermore, the longest treatment time was 6 h (i.e., 2 h shorter than in the first study), and 8,086 fewer progeny were scored at this time point than for the longest time point in the first study. It may be that the sample sizes were too

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TABLE 9-31

Summary of Mutagenicity Testing of EDC: Chromosomal Aberrations Tests

Reference	Test System	Chemical Information	Results	Comments
Shakarnis, 1969	Drosophila melanogaster X chromosome nondisjunction	Concentration tested: virgin Canton S females exposed to 0.7% EDC in 1.5 ℓ desiccator for 4 and 8 hours at 24-25°C. Source: Not given Purity: Not given	Statistically significantly (P<0.05) increases in exceptional female progeny for 4 hour exposure and male and female progeny for 8 hour exposure.	

0.07% EDC Duration of Treatment (h)	Normal Progeny No. Females	Normal Progeny No. Males	Exceptional Females No.	Exceptional Females %	Progeny Males No.	Progeny Males %
Control	5,848	5,727	0	0	0	0
4	24,125	21,297	8	0.03*	3	0.01
8	8,437	7,773	15	0.18*	7	0.09*

*P<0.05

TABLE 9-31 (cont.)

Reference	Test System	Chemical Information	Results	Comments
Shakarnis, 1970	Drosophila melanogaster X chromosome nondisjunction	Concentration tested: 3-day-old females from radiostable D-32 strain exposed to 0.07% EDC in a 1.5 ℓ desiccator for 4 or 6 hours at 24-25°C. Source: Not given Purity: Not given	Incidence of nondisjunction greater in treated group than in control. Increase not statistically significant.	1. Not as many individuals scored as in 1969 study. Sample size may not have been sufficiently large. 2. Longest exposure time 2 hours shorter than in previous experiment; may have been too short.

0.07% EDC Duration of Treatment (h)	Normal Progeny		Exceptional Females		Progeny Males	
	No. Females	No. Males	No.	%	No.	%
Control	2472	2205	0	0	1	0.03
4	3584	3401	1	0.03	1	0.03
6	4034	4090	4	0.10	3	0.07

TABLE 9-31 (cont.)

Reference	Test System	Chemical Information	Results	Comments
King et al. 1979	Micronucleus test: NMRI mice	Concentration tested: 2 i.p. injections of 4 mmoles/kg (400 mg/kg) given 24 hours apart. 4 animals/dose sacrificed after second injection. Source: Merck Co. Darmstadt, FRG Purity: Not specified, but melting point and elemental analysis were correct.	Negative	1. 1,000 polychromatic erythrocytes analyzed/animal. 2. Frequency of micronuclei not given.
Jenssen and Ramel, 1980	Micronucleus test: CBA mice	Concentration tested: single i.p. injection 100 mg/kg. Source: BDH Chemicals, Ltd. Purity: Not given	Negative. (0.15 ± 0.14) polycromatic erythocytes with micronuclei in controls v. 0.17 ± 0.10 in treated animals).	

small or the duration of exposure too short in the second study to be able to detect a statistically significant effect.

Micronucleus tests were performed by King et al. (1979) and Jenssen and Ramel (1980). Both studies reported negative results. King et al. (1979) injected NMRI mice with two intraperitoneal injections of 4 mmoles/kg (400 mg/kg) EDC (Merck Co., purity not specified but melting point (sic) and chemical analysis reported to be correct). The authors state this corresponds to an "approximate lethal dose" (the LD_{10} for intraperitoneal injections of EDC in mice is 250 mg/kg). The injections were given 24 h apart; the animals were killed 6 h after the second injection and bone marrow smears made. One thousand polychromatic erythrocytes (PCEs) were analyzed per animal. Frequencies of micronuclei were not given, but the results were evaluated to be negative by the authors.

Jenssen and Ramel (1980) also reported negative results in a micronucleus test. CBA mice were given a single intraperitoneal injection of EDC (DBH Chemicals Ltds., England, purity not given) at a dosage of 100 mg/kg. The animals were sacrificed the next day and PCEs (number not given) were scored for micronuclei. The frequencies of PCEs with micronuclei were 0.15 ± C.14 in the controls and 0.17 ± 0.10 in treated animals.

The positive response in the X-chromosome test in *Drosophila* (Shakarnis 1969) suggests EDC is capable of causing meiotic non-disjunction resulting in numerical chromosomal abnormalities. The negative responses obtained in the micronucleus tests may indicate that EDC does not cause chromosomal damage in mice. However, because EDC has not been adequately tested for its ability to cause structural chomosomal aberrations, it would be appropriate to perform mammalian *in vitro* and *in vivo* cytogenetic tests. Such testing is required before a judgment can be made on the ability of EDC to cause chromosomal aberrations.

OTHER EVIDENCE OF DNA DAMAGE

Three other tests have been conducted on the genotoxicity of EDC. These tests do not measure mutagenic events *per se* in that they do not demonstrate the induction of heritable (i.e., somatic or germinal) genetic alterations, but positive results in these test systems show that DNA has been damaged. Such test systems provide supporting evidence useful for assessing genetic risk.

Bacterial Test Systems

PolA Assay --

Ethylene dichloride has been reported positive in the *polA* assay which measures toxicity associated with unrepaired damage in DNA (Table 9-32). Brem et al. (1974) soaked sterile filter disks with 10 μℓ (80 μmoles) EDC. These were centered on the agar surface of petri dishes covered with bacteria (one set with *polA*$^+$ strain, the other with *polA*$^-$ strain). After incubation the plates were scored for differential inhibition of growth. An 8 mm zone of growth inhibition was observed in the polA$^+$ strain compared to a 9 mm zone of inhibition for the polA$^-$ strain. These repsonses were said to be reproducible. The ratio between the zones of inhibition (polA$^+$/polA$^-$) was 1.26 which is interpreted by the authors to be a positive response. However, it should be noted that 1 mm is not a big difference, and the ratio may be misleading.

Eukaryotic Test Systems

Unscheduled DNA Synthesis --

One test has been performed to assess the ability of EDC to cause unscheduled DNA synthesis (Perocco and Prodi 1981). Although demonstration that a chemical causes unscheduled DNA synthesis does not provide a measurement of its mutagenicity *per se*, it does indicate that the material damages DNA. Perocco and

TABLE 9-32

Summary of Mutagenicity Testing of EDC: PolA ASSAY

Reference	Test System	Strains	Activation System	Chemical Information	Results	Comments
Brem et al. 1974	polA differential cell killing assay	E. coli polA$^-$ polA$^+$	None	Concentration tested: 10 µl on filter disk	Questionable positive	1. All assays carried out in duplicate on at least three different occasions. 2. Only a small difference in diameter (i.e. 1 mm) was noted between the zones of killing in the two strains. Thus, the A$^+$/A$^-$ ratio may be misleading.

	Pol A Zone of Inhib.		
	A$^+$ mm	A$^-$ mm	A$^+$/A$^-$
EDC	8	9	1.26
MMS	45	54	1.44
Chloramphenicol	28	28	1.00

Prodi (1981) collected blood samples from healthy humans, separated the lymphocytes, and cultured 5 x 10^5 of them in 0.2 mℓ medium for 4 h at 37°C in the presence or absence of EDC (Carlo Erban, Milan, Italy or Merch-Schuchardt, Darmstadt, FRG, 97-99% pure). The tests were conducted both in the presence and in the absence of PCB-induced rat liver S9 mix. A comparison was made between treated and untreated cells for scheduled DNA synthesis (i.e., DNA replication) and unscheduled DNA synthesis. No difference was noted between the groups with respect to scheduled DNA synthesis measured as dpm of $[^3H]$ deoxythymidylic acid (TdR) after 4 h of culture (2661 ± 57 dpm in untreated cells compared to 2287 ± 60 dpm in cells treated with 5 μℓ/mℓ [0.06 μmole/mℓ] EDC). Subsequently 2.5, 5, and 10 μℓ/mℓ (0.03, 0.06 and 0.1 μmole/mℓ) EDC was added to cells which were cultured in 10 mM hydroxyurea to suppress scheduled DNA synthesis. The amount of unscheduled DNA synthesis was estimated by measuring dpm from incorporated $[^3H]$TdR 4 h later. At 10 μℓ/mℓ EDC 483 ± 37 and 532 ± 21 dpm were counted without and with exogenous metabolic activation, respectively. Both values were lower than corresponding negative controls of 715 ± 24 and 612 ± 26 dpm, respectively. No positive controls were run to ensure that the system was working properly although testing of chloromethyl methyl ether (CMME) with activation resulted in a doubling of dpms over the corresponding negative control values (1320 ± 57 at 5 μℓ/mℓ CMME versus 612 ± 26 untreated). The authors calculated an effective DNA repair value (r) for each chemical based on the control and experimental values with and without metabolic activation. Ethylene dichloride was evaluated by the authors as positive in the test, but they did not state their criteria for classifying a chemical as positive. It is important to note that none of the experimental values from cells treated with EDC without metabolic activation had higher dpm values than the controls. Furthermore, although two out of three experimental values were greater than the controls with metabolic activation

(673 ± 45 at 5 μℓ/mℓ and 630 ± 34 at 2.5 μℓ/mℓ compared to control value of 512 ± 26) the increases were not statistically significant. The positive finding reported in this work is therefore judged to be inconclusive.

Detection of DNA Adducts --

Reitz et al. (1982) compared the pharmacokinetics of EDC administered to Osborne-Mendel rats after inhalation and after exposure by gavage. (See section 9.1.3, especially 9.1.3.5.) As part of their study, DNA alkylation was measured in bacteria at EDC cytosol concentrations corresponding to those used in the DNA binding study (Table 9-33). Two gram aliquots of TA1535 were incubated with 7.06 μmol [^{14}C] EDC/mℓ (sp. act. = 3.2 mCi/mmol) and varying amounts of cytosol. DNA alyklation values at cytosol concentrations of 2.2, 7.8, 27, and 71% were 8.65, 27, 107, and 137 dpm/mg purified DNA, respectively. This corresponds to 4, 12.5, 49, and 64 alkylations x 10^{-6} DNA nucleotides. The corresponding reversion frequencies were 4.6 ± 0.82, 23.5 ± 3.0, 80.2 ± 9.6, and 111 ± 2.6, respectively (n = 3 in each case). A direct correlation between the degree of alkylation and an increase in mutation frequency was indicated by linear regression analysis (r = 0.9976). In the DNA alkylation studies with rats [^{14}C] EDC (sp. act. = 0.32 mCi/mmol) was administered to groups of three animals by gavage (150 mg/kg) or inhalation (150 ppm, 6 h). The animals were subsequently sacrificed and DNA was extracted from the liver, spleen, kidney, and stomach for measurement of DNA alkylation. Overall, there was three to five times more DNA alkylation after gavage than after inhalation. The values ranged from 5.8 ± 0.7 to 23.1 ± 7.4 alkylation/10^6 nucleotides for gavage versus 1.8 ± 0.3 to 8.2 ± 3.3 alkylation/10^6 nucleotides for inhalation. Under the conditions of test used in the experiments by Reitz et al. (1982) EDC exposure resulted in a similar degree of adduct formation in both rats and bacteria. Because DNA is the genetic material in both bacteria and rats, these data predict that mutations were induced in the

TABLE 9-33

Summary of Mutagenicity Testing of EDC: DNA Binding Studies

Reference	Test System	Strains	Activation System	Chemical Information			Comments
Reitz et al. 1982	DNA alkylation and mutagenesis in Salmonella	TA1535	Phenobarbital induced rat liver cytosol	% Cytosol	Revertants	Alkylation x 10^{-6} Nucleotides	1. Bacteria incubated with 7.06 µmol EDC/mℓ.
				2.2	4.6 ± 0.82	4	
				7.8	23.5 ± 3.0	12.5	2. Significant correlation between degree of alkylation and increased reversion frequency (r = 0.9976).
				27	80.2 ± 9.6	49	
				71	111 ± 2.6	64	
	DNA alkylation in rats	Osborne-Mendel rat	NA	Route of Exposure	Tissue	Alkylation x 10^{-6} Nucleotides (means from 2 experiments	3. Rats sacrificed 4 h post gavage or immediately after inhalation.
				Gavage 150 mg/kg	Liver	21.3 ; 13.9	4. Sp. act. 3.2 mCi/mmol for bacteria; 0.32 mCi/mmol for rats.
					Spleen	5.8 ; 2.5	
					Kidney	17.4 ; 14.5	
					Stomach	14.9 ; 6.7	
				Inhalation 150 ppm, 6 h	Liver	8.2 ; 3.3	
					Spleen	1.8 ; 1.8	
					Kidney	5.2 ; 2.0	
					Stomach	2.8 ; 1.9	

rat at the exposures used. This is in keeping with the positive responses in other eukaryotes including *Drosophila* and cultured CHO cells. DNA alkylation was not measured in rat gonads so it is not possible to estimate what the heritable genetic risk might be.

SUMMARY AND CONCLUSIONS

Ethylene dichloride (EDC) has been shown to cause gene mutations in bacteria, plants, *Drosophila* and cultured Chinese hamster ovary (CHO) cells. Weak positive responses were observed in the bacterial and CHO tests in the absence of an exogenous metabolic activation system. Stronger positive responses were found when hepatic metabolic activation systems were incorporated. Based on these positive findings in different test systems representing a wide range of organisms, EDC is judged to be capable of causing gene mutations.

EDC has been reported to cause meiotic chromosomal nondisjunction in *Drosophila*. The induction of meiotic nondisjunction is a significant genotoxic effect; however, a positive response in another test system is needed to permit a judgment on the generality of this effect. With respect to its ability to cause structural chromosomal aberrations, sufficient testing has not been performed. There is only one study on the ability of EDC to cause structural chromosomal aberrations (i.e. in *Allium* root tip cells and human lymphocytes). Because this study was reported in an abstract, the author's conclusions are unsubstantiated. Even though negative results are reported from micronucleus tests, additional information is needed to draw conclusions on the ability of EDC to cause chromosomal aberrations. For example, it would be appropriate to test EDC in *in vitro* and *in vivo* mammalian cytogenetic assays. A sister chromatid exchange assay would also be useful in assessing the ability of EDC to cause chromosome damage.

There are no available data on the ability of EDC to damage DNA in mammalian germ cells. Thus, studies on the ability of EDC to reach germinal tissue would be appropriate to determine whether EDC has the potential to cause heritable mutations which may contribute to the genetic disease burden. The finding that EDC causes heritable mutations in Drosophila and alkylates DNA in several somatic tissues in the rat reinforces the need for further germ cell studies in mammals.

Based on the weight-of-evidence, EDC is judged to be a weak direct-acting mutagen. Several of its putative metabolites, thought to be formed in mice and rats, are judged to be more potent mutagens (e.g., S-[2-chloroethyl]-L-cysteine or chloroacetaldehyde) than EDC with the potential to cause adverse effects in humans.

9.5 CARCINOGENICITY

The purpose of this section is to provide an evaluation of the likelihood that ethylene dichloride (EDC) (1,2-dichloroethane) is a human carcinogen and, on the assumption that it is a human carcinogen, to provide a basis for estimating its public health impact, including a potency evaluation in relation to other carcinogens. The evaluation of carcinogenicity depends heavily on animal bioassays and epidemiologic evidence. However, other factors, including mutagenicity, metabolism (particularly in relation to interaction with DNA), and pharmacokinetic behavior, have an important bearing on both the qualitative and quantitative assessment of carcinogenicity. The available information on these subjects is reviewed in other sections of this document. This section presents an evaluation of the animal bioassays, the human epidemiologic evidence, the quantitative aspects of assessment, and finally, a summary and conclusions dealing with all of the relevant aspects of the carcinogenicity of EDC.

9.5.1 Animal Studies

The carcinogenic potential of EDC has been investigated in a number of studies in which EDC was administered to rats and mice via various routes of administration. Five studies will be discussed: one gavage study performed by the National Cancer Institute (1978) in which EDC was administered to rats and mice; two inhalation studies, including one by Spencer et al. (1951) using rats, and one bioassay by Maltoni et al. (1980) in which EDC was administered to rats and mice; one intraperitoneal study by Theiss et al. (1977) in which EDC was administered to mice; and one skin-painting study by Van Duuren et al. (1979) in which EDC was administered to mice.

9.5.1.1 National Cancer Institute (1978) Rat Study--Hazleton Laboratories America Inc., Vienna, Virginia, under the sponsorship of the NCI, conducted a bioassay of 1,2-dichloroethane (EDC) using Osborne-Mendel rats. The NCI published a final report of the bioassay in 1978. Their results were also reported by Weisburger (1977), the International Agency for Research on Cancer (IARC 1979), and Ward (1980).

Technical-grade EDC, obtained for this study from the Dow Chemical Company, Midland, Michigan, was tested for its purity. Gas-liquid chromatography revealed a purity of 98% to 99% EDC with 4 to 10 minor peaks (Ward 1980). However, in the NCI bioassay a purity of greater than 90% was reported, with only two unidentified minor contaminants. Recently this discrepancy was resolved when the original sample of EDC was reanalyzed, at which time the EDC was found to be greater than 99% pure, with several unidentified contaminants. This analysis was also performed by the National Institute for Occupational Safety and Health (NIOSH) after completion of the bioassay; the sample contained about 99% 1,2-dichloroethane, with chloroform as the major contaminant (Hooper et al. 1980).

Solutions of EDC were prepared in corn oil and administered by oral intubation to 200 Osborne-Mendel rats starting at 8 weeks of age. The design summary of this experiment is given in Table 9-34. On the basis of a subchronic EDC study, 50 rats of each sex were used for each of two dose levels in the chronic study. The maximum tolerated dose (MTD) was determined to be 95 mg/kg/day for both males and females; the second dose was one-half the MTD (47 mg/kg/day).

Twenty animals of each sex served as untreated controls; an equal number were given the vehicle (corn oil) by gavage. Because of the inadequacies of the subchronic studies, the initial doses administered to the test animals were

TABLE 9-34. DESIGN SUMMARY FOR 1,2-DICHLOROETHANE (EDC) GAVAGE EXPERIMENT IN OSBORNE-MENDEL RATS (NCI 1978)

Group	Initial number of animals	1,2-dichloroethane dosage[a]	Observation period		Time-weighted average dosage over a 78-week period[b]
			Treated (weeks)	Untreated (weeks)	
Males					
Untreated control	20	---	---	106	---
Vehicle-control	20	0	78	32	0
Low-dose	50	50	7	---	47
		75	10	---	---
		50	18	---	---
		50[c]	34	9	---
		0	---	32	---
High-dose[d]	50	100	7	---	95
		150	10	---	---
		100	18	---	---
		100[c]	34	9	---
		0	---	23	---
Females					
Untreated control	20	---	---	106	---
Vehicle-control	20	0	78	32	0
Low-dose	50	50	7	---	47
		75	10	---	---
		50	18	---	---
		50[c]	34	9	---
		0	---	32	---
High-dose[d]	50	100	7	---	95
		150	10	---	---
		100	18	---	---
		100[c]	34	9	---
		0	---	15	---

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[a] Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

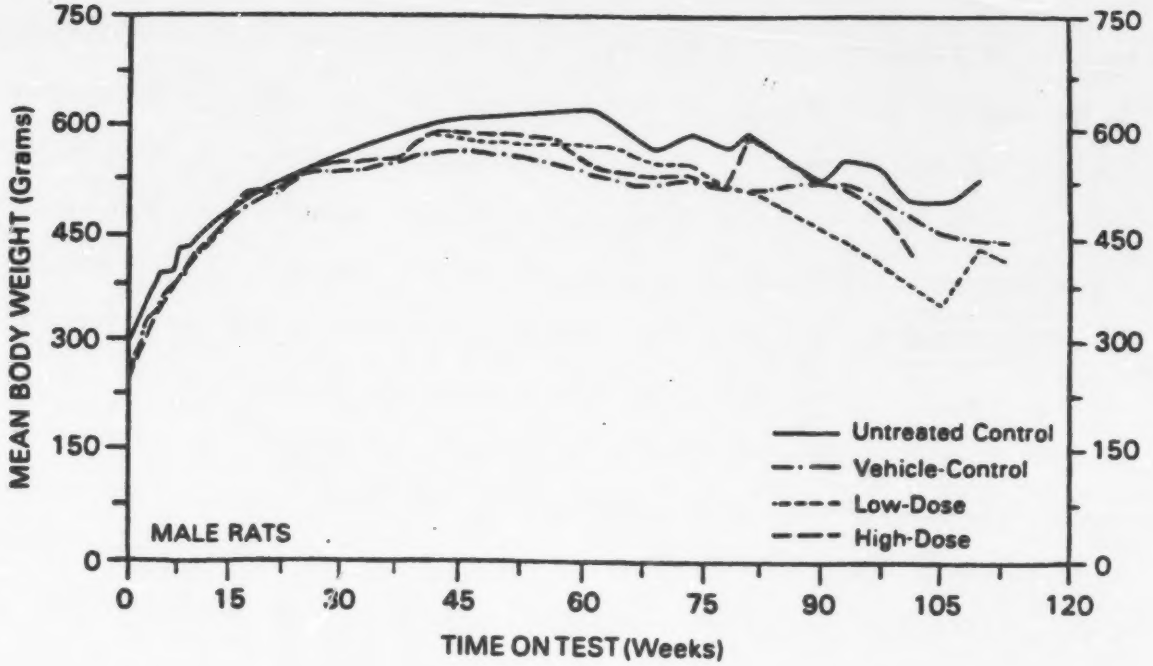
[b] Time-weighted average dosage = $\frac{(\text{dosage x weeks received})}{78 \text{ weeks}}$

[c] These dosages were cyclically administered with a pattern of one dosage-free week followed by 4 weeks (5 days per week) of dosage at the level indicated.

[d] All animals in this group died before the bioassay was terminated.

found to be inappropriate. Early signs of toxicity necessitated several changes in the dosages (Table 9-34). Animal weight and food consumption per cage were obtained weekly for the first 10 weeks and monthly thereafter. Animals were checked daily for mortality. Weight depression was observed in both groups exposed to EDC. By 50 weeks, the weight depression averaged 12% in high-dose rats (Figure 9-8). Mortality was early and severe in dosed animals, especially those given the highest doses. The mean survival was approximately 55 weeks on test for high-dose males and females (Figure 9-9 and Table 9-35). The early deaths were usually not due to cancer; rather, the toxic effects of EDC appeared to be responsible for these deaths. Rats dying early had a variety of lesions, including bronchopneumonia and endocardial thrombosis, which may have contributed to early death. The pneumonia may have been the result of a viral, bacterial, or mycoplasmal infection, and the exposure to the chemical may have increased the tendency to develop severe pulmonary lesions, which would lead to death. For the high-dose male rats, 50% (25/50) were alive at week 55 and 16% (8/50) were alive at week 75. Survival was higher in the other groups; 52% (26/50) of the rats in the low-dose group lived at least 82 weeks, and 50% (10/20) in the vehicle-control group lived at least 72 weeks. In the high-dose female rats, 50% (25/50) were alive at week 57; 20% (10/50) of the rats in the low-dose group were alive at week 85. Despite the sacrifice of five females at week 57, 65% (13/22) of the untreated control group survived until the end of the study.

A gross necropsy was performed on each animal that died during the experiment or was killed at the end. A total of 28 organs, plus any tissues containing visible lesions, were fixed in 10% buffered formalin, embedded in paraplast, and sectioned at 5 u for slides. Hematoxylin and eosin stain were used routinely, and other stains were employed when necessary. Diagnoses of tumors



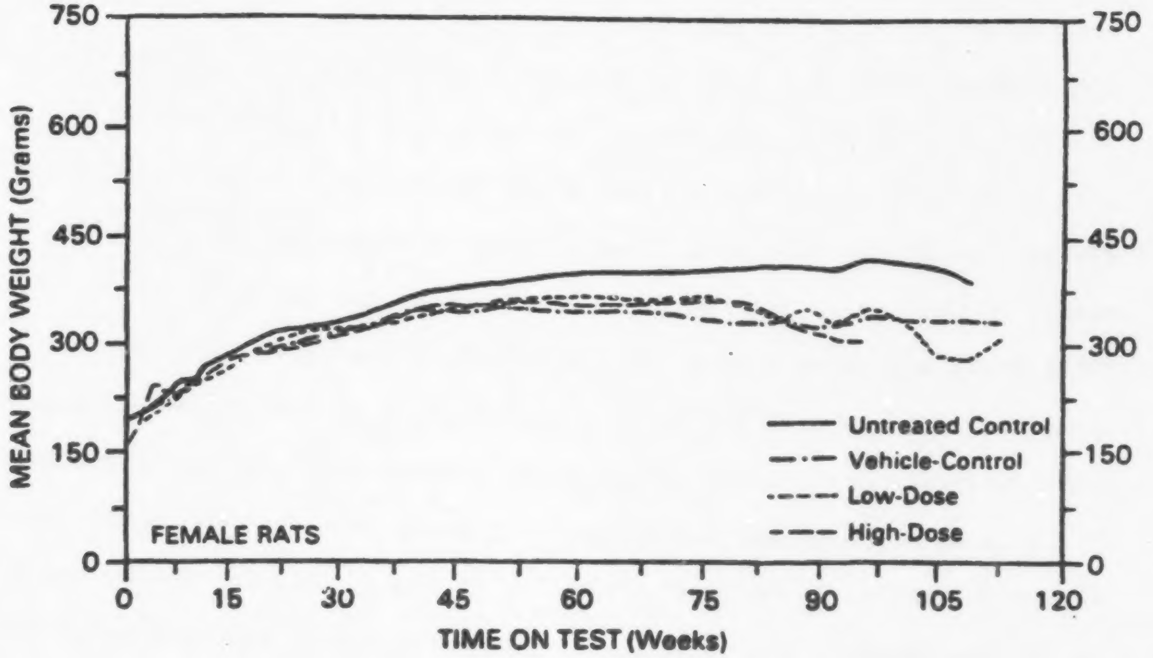
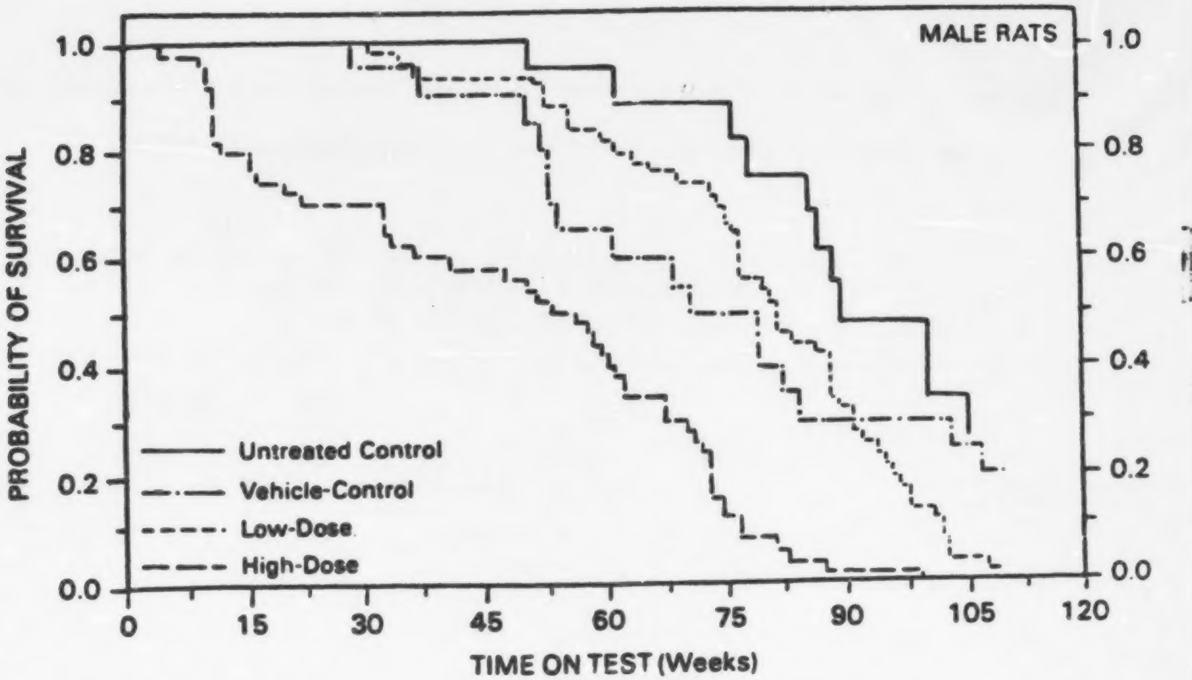


Figure 9-8 . Growth curves for male and female Osborne-Mendel rats administered 1,2-dichloroethane (EDC) by gavage. (NCI 1978)



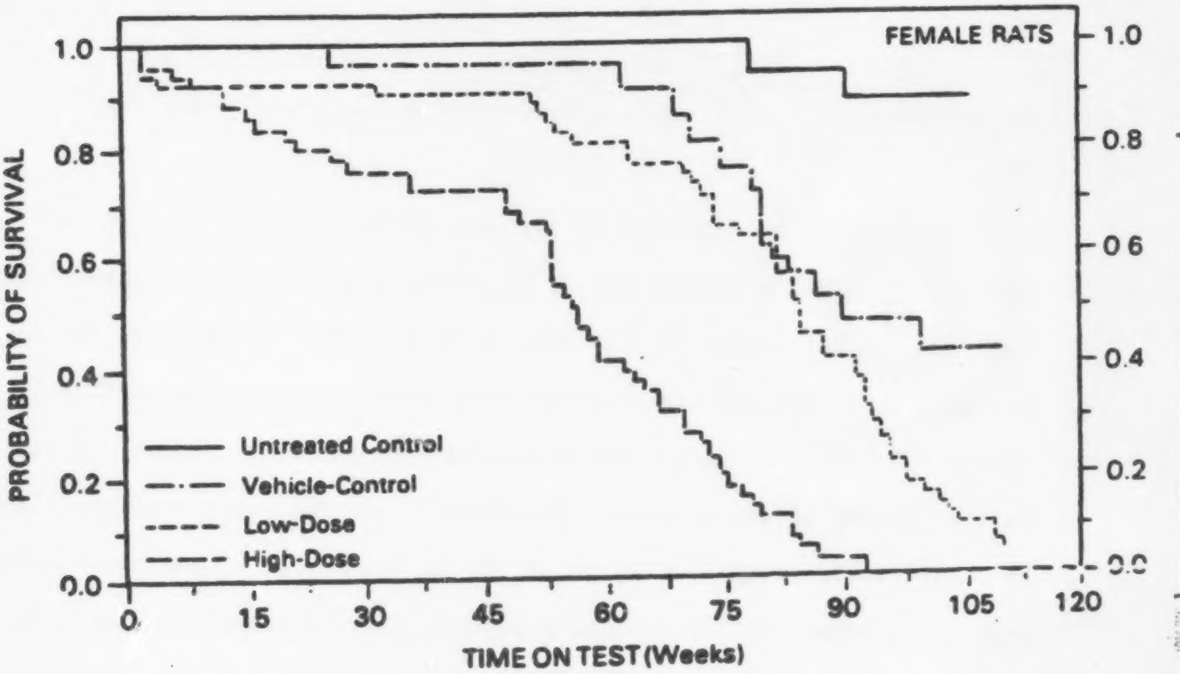


Figure 9-9 . Survival comparisons for male and female Osborne-Mendel rats administered 1,2-dichloroethane (EDC) by gavage. (NCI 1978) and other lesions were coded according to the Systematized Nomenclature of Pathology (SNOP) of the College of American Pathologists (1965).

TABLE 9-35 . TERMINAL SURVIVAL OF OSBORNE-MENDEL RATS
TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

	Males		Females	
Group	Weeks in study	Animals alive at end of study	Weeks in study	Animals alive at end of study
Untreated control	106	4/20[a] (20%)	106	13/20[a] (65%)
Vehicle-control	110	4/20 (20%)	110	8/20 (40%)
Low-dose	110	1/50 (2%)	101	1/50 (2%)
High-dose	101	0/50[b] (0%)	93	0/50[b] (0%)

[a] Five rats were sacrificed at 75 weeks.
[b] All animals in this group died before the bioassay was terminated.

Squamous cell carcinomas of the forestomach occurred in 3/50 (6%) low-dose males, 9/50 (18%) high-dose males, 0/50 (0%) high-dose females, and 1/49 (2%) low-dose females (Table 9-36). None of these tumors occurred in the controls. For male rats, the Cochran-Armitage Trend Test indicated a significant ($P = 0.01$) positive association between dosage and the incidence of squamous cell carcinoma of the stomach. The Fisher Exact Test confirmed the significance of these results with P values of 0.039 and 0.001 when comparisons were made with the matched vehicle-control group and the pooled vehicle-control* group, respectively.

Squamous cell carcinomas of the forestomach were first observed in high-dose male rats at 51 weeks after oral intubation of EDC. These lesions were characterized microscopically by acanthosis and hyperkeratosis in the superficial area. The basal epithelial layer contained papillary cords and nests of anaplastic squamous epithelium supported by a dense band of fibrous connective tissue. These carcinomas extended through the muscularis mucosa, submucosa, muscular layers, and serosa, and in one high-dose male, metastasized to adjacent tissues.

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*The pooled vehicle-control group combined the vehicle-controls from the studies of 1,2-dichloroethane, 1,1,2-trichloroethane, and trichloroethane.

TABLE 9-36. SQUAMOUS CELL CARCINOMAS OF THE FORESTOMACH IN OSBORNE-MENDEL RATS TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

Group	Males	P value[a]	Females	P value[a]
Untreated control	0/20 (0%)		0/20 (0%)	
Matched vehicle-control	0/20 (0%)		0/20 (0%)	
Pooled vehicle-control	0/60 (0%)		0/59 (0%)	
Low-dose	3/50 (6%)	NS	1/49 (2%)	NS
High-dose	9/50 (18%)[b]	0.001	0/50 (0%)	NS

[a] P values calculated using the Fisher Exact Test. Treated versus pooled vehicle-control.

[b] A squamous cell carcinoma of the forestomach metastasized in one male in this group.

NS = not significant when P values are greater than 0.05.

Hemangiosarcomas were noted in some treated rats, as described in Table 9-37, but not in any of the controls. Low-dose males and females showed higher incidences of hemangiosarcoma than high-dose animals. Tumors were observed in several sites, including spleen, liver, adrenal glands, pancreas, large intestine, subcutaneous tissue, and abdominal cavity. The Cochran-Armitage Trend Test indicated a significant (P = 0.021) positive association between dosage and the incidence of hemangiosarcomas in male rats as compared to the pooled vehicle-control rats; the trend was also positive in female rats (P = 0.042). The Fisher Exact Test confirmed these findings, with statistically significant P values for high-dose males versus pooled vehicle-controls (P = 0.016), for low-dose males versus pooled vehicle-controls (P = 0.003), and for both low- and high-dose females versus pooled vehicle-controls (P = 0.041).

Table 9-37. HEMANGIOSARCOMAS IN OSBORNE-MENDEL RATS TREATED WITH 1,2-DICHLOROETHANE (EDC) (adapted from NCI 1978)

Group	Males	P value[a]	Females	P value[a]
Untreated control	0/20 (0%)		0/20 (0%)	
Matched vehicle-control	0/20 (0%)		0/20 (0%)	
Pooled vehicle-control	1/60 (2%)		0/59 (0%)	
Low-dose[b]	9/50 (18%)	0.003	4/50 (8%)	0.041
High-dose[c]	7/50 (14%)[b]	0.016	4/50 (8%)	0.041

[a] P values calculated using the Fisher Exact Test (one-tailed). Treated versus pooled vehicle-control.

[b] Only 48 animals were examined for hemangiosarcomas of the large intestine.

[c] Only 49 animals were examined for hemangiosarcomas of the spleen and adrenals and 48 for hemangiosarcomas of the pancreas.

NS = Not significant.

In addition to stomach carcinomas and hemangiosarcomas, EDC-treated female rats showed significant increases in the incidence of mammary adenocarcinomas (Table 9-38). Tumors were observed in the high-dose group as early as 20 weeks after treatment. The Cochran-Armitage Trend Test detected a significant (P<0.001) positive association between the dosage and the incidence of mammary adenocarcinomas when compared with either control group. This tumor incidence was significant when the high-dose group was compared with either the matched vehicle-control group (P<0.001) or the pooled vehicle-control group (P=0.002) using the Fisher Exact Test. Historically, this tumor was observed in 4/200 (2%) of the vehicle-control females.

TABLE 9-38. ADENOCARCINOMAS OF THE MAMMARY GLAND IN FEMALE OSBORNE-MENDEL RATS TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

Group	Adenocarcinoma of the mammary gland	P value[a]
Untreated control	2/20 (10%)	
Matched vehicle-control	0/20 (0%)	
Pooled vehicle-control	1/59 (2%)	
Low-dose	1/50 (2%)	NS
High-dose	18/50 (36%)	0.0008

[a] P values calculated using the Fisher Exact Test (one-tailed). Treated versus pooled vehicle-control.
NS = Not significant.

An increased incidence of fibromas of the subcutaneous tissue was reported in both high-dose (P = 0.007) and low-dose (P = 0.017) male rats when compared to the pooled vehicle-control group.

In summary, a statistically significant increase in the incidence of squamous cell carcinomas of the forestomach, hemangiosarcomas of the circulatory system, and fibromas of the subcutaneous tissue occurred in male rats. There was also a statistically signif increase in the incidence of adenocarcinomas of mammary gland and hemangiosarcomas of the circulatory system in female rats.

9.5.1.2. National Cancer Institute (1978) Mouse Study -- Hazleton Laboratories America Inc., under the sponsorship of the NCI, conducted a bioassay of 1,2-dichloroethane (EDC) using B6C3F1 mice. The results of this study were published by the NCI (1978) and were also reported by Weisburger (1977), the International Agency for Research on Cancer (IARC, 1979), and Ward (1980).

Technical-grade EDC (with the same purity as that described in the NCI rat study) was administered to 200 B6C3F1 mice starting at 5 weeks of age. The design summary for this experiment is given in Table 9-39. On the basis of results of the subchronic studies, 50 mice of each sex were used at each of the two dose levels for the chronic study. The MTD was determined to be 195 mg/kg/day for male mice and 299 mg/kg/day for female mice. The second dose, which was one-half the MTD, was determined to be 97 mg/kg/day for male mice and 149 mg/kg/day for female mice.

Twenty mice of each sex served as untreated controls, and an equal number were given the vehicle (corn oil) by gavage. Because of inadequacies in the subchronic studies, the initial doses administered to the test animals were found to be inappropriate. Signs of toxicity in these animals early in the study led to changes of the dosages several times (Table 9-40). Animal weights and food consumption were recorded for the first 10 weeks and monthly thereafter. Animals were checked daily for mortality and signs of toxic effects. No dose-related mean body weight depression was observed in male mice or low-dose female mice (Figure 9-10). A depression in the mean body weight of the high-dose female mice was apparent as early as week 15. The estimated probabilities of survival for male and female mice in the control and EDC-dosed groups are shown in Figure 9-11. Terminal survival of treated and control mice is shown in Table 9-40. For male mice, no statistically significant association between dosage and mortality was observed. In the high-dose group, 50% (25/50) of the mice were alive at 84 weeks and 42% (21/50) survived until the end of the study. In a low-dose group, however, survival was low. By 24 weeks, 52% (26/50) of the low-dose group and 55% (11/20) of the untreated control group

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TABLE 9-39. DESIGN SUMMARY FOR 1,2-DICHLOROETHANE (EDC) GAVAGE EXPERIMENT IN B6C3F1 MICE (adapted from NCI 1978)

Group	Initial number of animals	1,2-dichloroethane dosage[a]	Observation period		Time-weighted average dosage[b]
			Treated (weeks)	Untreated (weeks)	
Males					
Untreated control	20	---	---	90	---
Vehicle-control	20	0	78	12	0
Low-dose	50	75	8	---	97
		100	70	---	---
		0	---	12	---
High-dose	50	150	8	---	195
		200	70	---	---
		0	---	13	---
Females					
Untreated control	20	---	---	91	---
Vehicle-control	20	0	78	32	0
Low-dose	50	125	8	---	149
		200	3	---	---
		150	67	---	---
		0	---	13	---
High-dose	50	250	8	---	299
		400	3	---	---
		300	67	---	---
		0	---	13	---

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[a] Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

[b] Time-weighted average dosage = $\frac{\text{(dosage x weeks received)}}{\text{weeks receiving chemical}}$

had died. In the high-dose group, 72% (36/50) of the animals died between weeks 60 and 80. These deaths may have been tumor-related, since 69% (25/36) had one or more tumors. Survival was high in the other groups; 68% (35/50) of the low-dose and 80% (16/20) of the untreated control groups survived until the end of the study.

TABLE 9-40. TERMINAL SURVIVAL OF B6C3F1 MICE TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

	Males		Females	
Group	Weeks in study	Animals alive at end of study	Weeks in study	Animals alive at end of study
Untreated control	90	7/20 (35%)	90	16/20 (80%)
Vehicle-control	90	11/20 (55%)	90	16/20 (80%)
Low-dose	90	11/50 (22%)	91	34/50 (68%)
High-dose	91	21/50 (42%)	91	1/50 (2%)

A gross necropsy was performed on each animal that died during the experiment or was killed at the end. Twenty-eight organs in all, plus any tissues containing visible lesions, were fixed in 10% buffered formalin, embedded in paraplast, and sectioned at 5 u for slides. Hematoxylin and eosin stain were used routinely, with other stains employed as necessary. Diagnoses of tumors and other lesions were coded according to the Systematized Nomenclature of Pathology (SNOP) of the College of American Pathologists.

The histopathologic findings of the study concerning hepatocellular carcinomas in mice are tabulated in Table 9-41. Hepatocellular carcinomas occurred in 2/17 (12%) untreated control males, 1/19 (5%) low-dose males, and

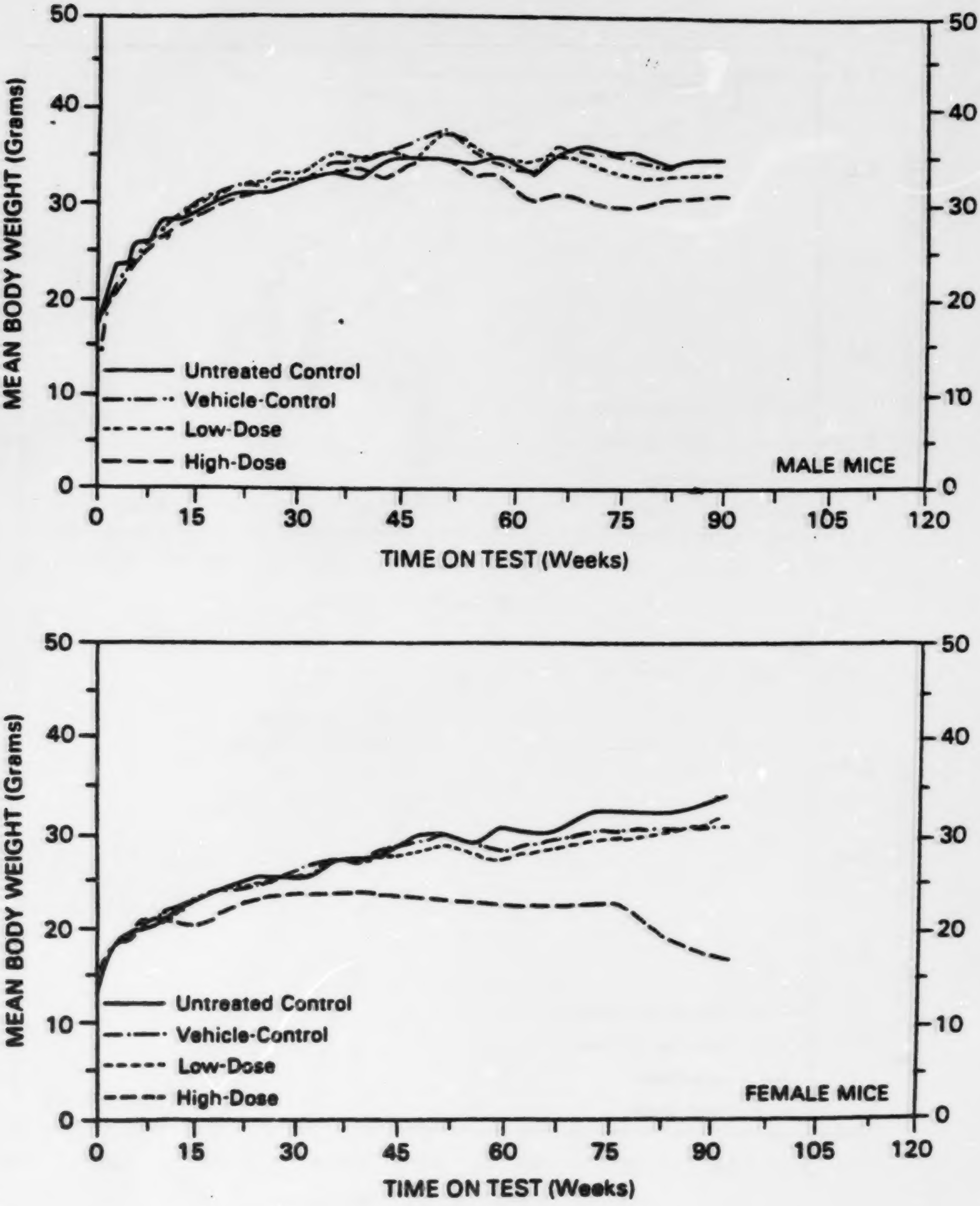

Figure 9-10· Growth curves for male and female B6C3F1 mice administered 1,2-dichloroethane (EDC) by gavage. (NCI 1978)'

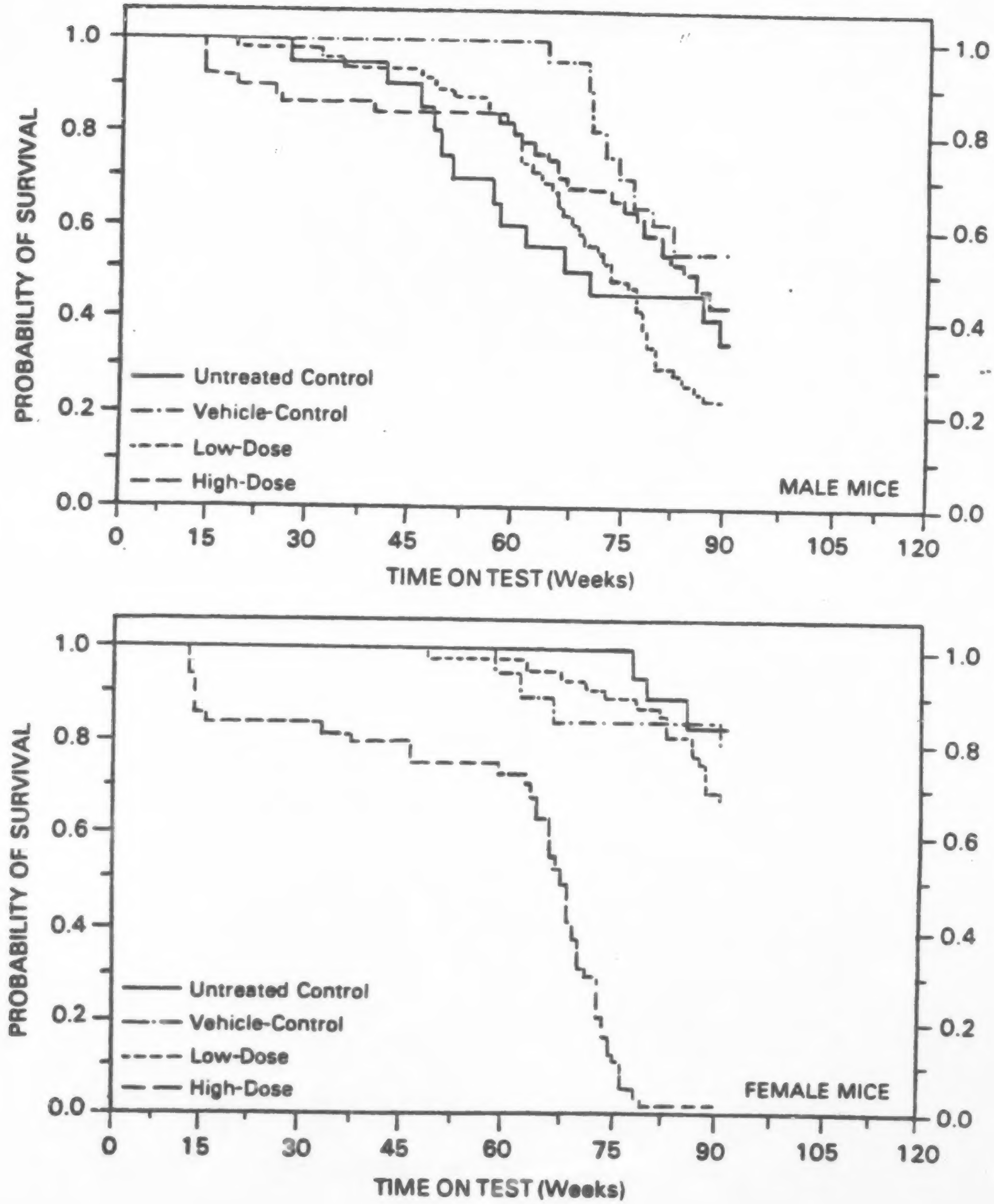

Figure 9-11. Survival comparisons for male and female B6C3F1 mice given 1,2-dichloroethane (EDC) by gavage. (NCI 1978)

12/48 (25%) high-dose males. A significant number of hepatocellular carcinomas were observed in high-dose males. The Cochran-Armitage Trend Test indicated a positive dose-response association when the high-dose group was compared with either the matched vehicle-controls (P = 0.025) or the pooled vehicle-controls (P = 0.006). The Fisher Exact Test supported this finding with a significant (P = 0.009) comparison of the high-dose to the pooled control group.

TABLE 9-41. HEPATOCELLULAR CARCINOMAS IN B6C3F1 MICE TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

Group	Males	P value[a]	Females	P value[a]
Untreated controls	2/17 (12%)		0/19 (0%)	
Matched vehicle-controls	1/19 (5%)		1/20 (5%)	
Pooled vehicle-controls	4/59 (7%)			
Low-dose	6/47 (13%)	NS	0/50 (0%)	NS
High-dose	12/48 (25%)	0.009	1/47 (2%)	NS

[a] P values calculated using the Fisher Exact Test (one-tailed). Treated versus pooled vehicle-control.
NS = not significant.

A large number of alveolar/bronchiolar adenomas were found in mice treated with EDC (Table 9-42); 31% in both male (15/48) and female (15/48) high-dose mice. These adenomas were not observed in untreated or vehicle-control males. For both sexes the Cochran-Armitage Trend Test showed a significant (P = 0.005) positive dose-response association when the dosed groups were compared to either control group. The Fisher Exact Test also indicated that the high-dose group for both sexes had significantly higher (P = 0.016)

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incidence rates than either of the two control groups. For female mice, the Fisher Exact Test comparing the low-dose group to the pooled vehicle-control group was also statistically significant (P = 0.046).

TABLE 9-42. ALVEOLAR/BRONCHIOLAR ADENOMAS IN B6C3F1 MICE TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

Group	Males	P value[a]	Females	P value[a]
Untreated controls	0/20 (0%)		1/19 (5%)	
Matched vehicle-controls	0/19 (0%)		1/20 (5%)	
Pooled vehicle-controls	0/59 (3%)		2/60 (3%)	
Low-dose	1/47 (2%)	NS	7/50 (14%)	0.046
High-dose[b]	15/48 (31%)	0.0025	15/48 (31%)	0.0201

[a] P values calculated using the Fisher Exact Test (one-tailed). Treated versus pooled vehicle-control.
[b] In addition, one high-dose female mouse had an alveolar/bronchiolar carcinoma.
NS = not significant.

Squamous cell carcinomas of the forestomach occurred in 1/19 (5%) vehicle-control males, 1/46 (2%) low-dose females, and 5/48 (10%) high-dose females (Table 9-43). For female mice, the Cochran-Armitage Trend Test indicated a significant (P = 0.035) positive association between dosage and the incidence of squamous cell carcinomas of the forestomach when comparing the dosed groups to the pooled vehicle-controls. The Fisher Exact Test, however, was not significant. The microscopic appearance of the stomach of mice was comparable to that described for rats.

TABLE 9-43. SQUAMOUS CELL CARCINOMAS OF THE FORESTOMACH IN B6C3F1 MICE TREATED WITH 1,2-DICHLOROETHANE (EDC) (adapted from NCI 1978)

Group	Males	P value[a]	Females	P value[a]
Untreated control	0/20 (0%)		0/20 (0%)	
Matched vehicle-control	1/19 (5%)		1/20 (5%)	
Pooled vehicle-control	1/59 (2%)		1/60 (2%)	
Low-dose	1/46 (2%)	NS	2/50 (4%)	NS
High-dose	2/50 (4%)	NS	5/48 (10%)	NS

[a] P values calculated using the Fisher Exact Test (one-tailed). Treated versus vehicle-control.
NS = not significant.

The incidence of adenocarcinomas of the mammary gland in female mice treated with EDC is presented in Table 9-44 . The Cochran-Armitage Trend Test indicated a significant (P = 0.007) positive association between dosage and the incidence of adenocarcinomas of the mammary gland when compared to the pooled controls. The Fisher Exact Test confirmed these results with a significant ($P \leq 0.003$) comparison of both high-dose (7/48) and low-dose (9/50) groups to the pooled vehicle-control groups (0/60).

Endometrial tumors observed in female mice are described in Table 9-45 . The Cochran-Armitage Trend Test indicated a significant (P = 0.017) positive association between dosage and combined incidence. The Fisher Exact Test showed a statistically significant (P = 0.014) incidence in the high-dose (5/47) group.

TABLE 9-44. ADENOCARCINOMAS OF THE MAMMARY GLAND IN FEMALE B6C3F1 MICE TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

Group	Adenocarcinoma of the mammary gland	P value[a]
Pooled vehicle-control	0/60 (0%)	
Matched vehicle-control	0/20 (0%)	
Low-dose	9/50 (18%)	0.0005
High-dose	7/48 (15%)	0.0026

[a] P values calculated using the Fisher Exact Test (one-tailed). Treated versus pooled vehicle-control.

TABLE 9-45. ENDOMETRIAL POLYP OR ENDOMETRIAL STROMAL SARCOMAS IN FEMALE B6C3F1 MICE TREATED WITH 1,2-DICHLOROETHANE (EDC)
(adapted from NCI 1978)

Group	Endometrial polyp or endometrial stromal sarcomas	P value[a]
Pooled vehicle-control	0/60 (0.0%)	
Matched vehicle-control	0/20 (0.0%)	
Low-dose	5/49 (10.0%)	0.016
High-dose	5/47 (11.0%)	0.014

[a] P values calculated using the Fisher Exact Test (one-tailed). Treated versus pooled vehicle-control.

In summary, the NCI study in B6C3F1 mice demonstrated a statistically significant increase in incidences of hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice and a statistically significant increase in incidences of alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice.

9.5.1.3 Spencer et al. (1951) Rat Study--An early inhalation study conducted by Spencer et al. (1951) found no evidence of carcinogenic activity when 15 male and 15 female Wistar rats were exposed 151 times during a 212-day period to EDC at 200 ppm for 7 hours per exposure.

9.5.1.4 Maltoni et al. (1980) Rat Study--A more recent inhalation study conducted by Maltoni et al. (1980) in Sprague-Dawley rats provided no evidence of carcinogenicity after lifetime exposure to EDC. The EDC used in this study was supplied by Montedison, and had a purity of 99.82%, with five contaminants (Table 9-46). The design of the experiment is given in Table 9-47 .

TABLE 9-46 . CHARACTERIZATION OF 1,2-DICHLOROETHANE (EDC) INHALATION EXPERIMENT IN SPRAGUE-DAWLEY RATS
(Maltoni et al. 1980)

Component	Purity
1,2-Dichloroethane	99.82%
1,1-Dichloroethane	0.02%
Carbon tetrachloride	0.02%
Trichloroethylene	0.02%
Perchloroethylene	0.03%
Benzene	0.09%

TABLE 9-47 . DESIGN SUMMARY FOR 1,2-DICHLOROETHANE (EDC) EXPERIMENT IN SPRAGUE-DAWLEY RATS[a]

(Maltoni et al. 1980)

		Animals[b]	
Group	Concentration	Sex	Number
I	250-150 ppm[c]	M	90
		F	90
II	50 ppm	M	90
		F	90
III	10 ppm	M	90
		F	90
IV	5 ppm	M	90
		F	90
V	Controls in chambers	M	90
		F	90
VI	Controls	M	90
		F	90

[a] Exposed 7 hours/day, 5 days/week, for 78 weeks.

[b] Sprague-Dawley rats, 12 weeks old at start.

[c] After a few weeks the dose was reduced to 150 ppm, because of high toxicity at the 250 ppm level.

Maltoni et al. exposed four groups of 12-week-old Sprague-Dawley rats (each group consisting of 180 rats of both sexes) to EDC concentrations of 250-150 ppm, 50 ppm, 10 ppm, and 5 ppm, respectively, 7 hours per day, 5 days per week, for 78 weeks. After several days of 250 ppm exposure, the rats began to exhibit severe toxic effects, and the concentration was reduced to 150 ppm. Two groups, composed of 180 rats per group, served as controls. One of the two control groups was kept in an exposure chamber under the same conditions and for the same length of time as the exposed rats. At the end of the treatment period, the animals were allowed to live until spontaneous death. Animals were weighed every 2 weeks during the treatment period and every 8 weeks thereafter. All detectable gross pathologic changes were recorded. A complete autopsy was performed on each animal, with histopathologic examinations conducted on the following: brain, Zymbal glands, retrobulbar glands, interscapular brown fat, salivary gland, tongue, lungs, thymus, diaphragm, liver, pancreas, kidneys, spleen, stomach, various segments of the intestine, bladder, gonads, lymph nodes (axillary, inguinal, and mesenteric), and any other organ with pathologic lesions.

The extent of mortality varied with the different groups, but there appears to be no direct relationship between mortality and exosure to EDC (Table 9-48). The highest survival rate was observed in both males and females of the group exposed to EDC at 5 ppm. In females the highest mortality rate was observed in the control group in the chamber and in the group exposed to EDC at 250-150 ppm. The survival rates at 52 and 104 weeks of age are reported in Table 9-48 . At these ages the overall survival rates were 93.9% and 27.3%, respectively. The survival rates after 52 weeks from the start of the experiment are also given in Table 9-48 . The overall survival rate was 83.7%.

The results of histopathologic analysis are shown in Table 9-49 . No statistically significant increase in the incidence of any specific type of tumor was found in the treated rats when compared with controls. There was, however, an increased incidence of mammary tumors in some rats in Group IV, particularly when compared with the control group in the chamber (Table 9-50).

It appears that the increase in mammary tumors in some of the treated groups, particularly when compared to controls in the chamber, was not due to malignant tumors, but to fibromas and fibroadenomas. The increased incidence of mammary fibromas and fibroadenomas is statistically significant in groups exposed to EDC at 250-150 ppm, 50 ppm, and 5 ppm, when compared to controls in the

TABLE 9-48. SURVIVAL OF SPRAGUE-DAWLEY RATS EXPOSED TO EDC AT 52 AND 104 WEEKS[a] (Maltoni et al. 1980)

Group	Dose (ppm)	Sex	Initial numbers	Survivors at 52 weeks of age		Survivors at 104 weeks of age		Survivors after 52 weeks from start of study	
				Number	Percent	Number	Percent	Number	Percent
I	250–150[b]	M	90	79	87.8	10	11.1	67	74.4
		F	90	84	93.3	21	23.3	79	87.8
II	50	M	90	87	96.7	17	18.9	70	77.8
		F	90	87	96.7	29	32.2	84	93.3
III	10	M	90	81	90.0	13	14.4	70	77.8
		F	90	87	96.7	26	28.9	81	90.0
IV	5	M	90	89	98.9	45	50.0	75	83.3
		F	90	90	100.0	48	53.3	85	94.4
V	Controls in chambers	M	90	80	88.9	12	13.3	64	71.1
		F	90	79	87.8	22	24.4	73	81.1
VI	Controls	M	90	83	92.2	16	17.8	72	80.0
		F	90	88	97.8	36	40.0	84	93.3

[a] Rats were 12 weeks old at the start of the experiment.

[b] After a few weeks the dose was reduced to 150 ppm because of high toxicity at the 250 ppm level.

TABLE 9-49 TUMOR INCIDENCE IN SPRAGUE-DAWLEY RATS EXPOSED TO EDC
(Maltoni et al. 1980)

		Animals[a]				Animals with tumors										
						Mammary tumors		Zymbal gland carcinomas			Leukemias			Nephroblastomas		
Group	Concentration	Sex	Number at start	Corrected number	Total number	Percent[b]	Average latency time (wk)[c]	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]
I	250-150 ppm[e]	M	90	89	11	12.3	92.9	0	---	---	0	---	---	0	---	---
		F	90	90	52	57.7	78.6	2	2.2	78.0	0	---	---	0	---	---
		M and F	180	179	63	35.2	81.1	2	1.1	78.0	0	---	---	0	---	---
II	50 ppm	M	90	90	10	11.1	88.8	0	---	---	1	1.1	80.0	0	---	---
		F	90	90	58	64.4	78.5	1	1.1	86.0	2	2.2	75.5	0	---	---
		M and F	180	180	68	37.8	80.0	1	0.6	86.0	3	1.7	76.3	0	---	---
III	10 ppm	M	90	89	5	5.6	60.8	0	---	---	4	4.6	76.0	0	---	---
		F	90	90	43	47.8	79.4	0	---	---	0	---	---	0	---	---
		M and F	180	179	48	26.8	77.5	0	---	---	4	2.2	76.0	0	---	---
IV	5 ppm	M	90	90	11	12.2	110.2	0	---	---	2	2.2	133.5	1	1.1	85.0
		F	90	90	65	72.2	83.2	2	2.2	47.0	6	6.7	83.5	0	---	---
		M and F	180	180	76	42.2	87.1	2	1.1	47.0	8	4.4	96.0	1	0.7	84.0
V	Controls in chambers	M	90	90	8	8.9	85.5	1	1.1	78.0	1	1.1	37.0	0	---	---
		F	90	90	38	42.2	83.1	0	---	---	3	3.3	64.3	0	---	---
		M and F	180	180	46	25.5	83.6	1	0.6	78.0	4	2.2	59.5	0	---	---
VI	Controls	M	90	90	5	5.5	92.0	1	1.1	74.0	0	---	---	0	---	---
		F	90	90	52	57.8	85.5	0	---	---	3	3.3	79.3	0	---	---
		M and F	180	180	57	31.7	86.1	1	0.6	74.0	3	1.7	79.3	0	---	---
Total			1080	1070												

(continued on the following page)

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TABLE 9-49. (Continued)

			Animals with tumors											
			Angiosarcomas						Angiomas and fibroangiomas					
			Liver			Other Sites			Liver			Other sites		
Group	Concentration	Sex	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]
I	250-150 ppm[e]	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
II	50 ppm	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
III	10 ppm	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
IV	5 ppm	M	0	---	---	0	---	---	0	---	---	1	1.1	125.0
		F	0	---	---	0	---	---	0	---	---	1	1.1	131.0
		M and F	0	---	---	0	---	---	0	---	---	2	1.1	128.0
V	Controls in chambers	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
VI	Controls	M	0	---	---	0	---	---	0	---	---	1	1.1	130.0
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	1	0.7	130.0

(continued on the following page)

TABLE 9-49. (Continued)

			Animals with tumors											
			Hepatomas			Forestomach epithelial			Skin carcinomas			Subcutaneous sarcomas		
Group	Concentration	Sex	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Average latency time (wk)[d]
I	250-150 ppm[c]	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
II	50 ppm	M	0	---	---	1	1.1	60.0	1	1.1	56.0	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	1	0.6	60.0	1	0.6	56.0	0	---	---
III	10 ppm	M	0	---	---	0	---	---	1	1.1	94.0	0	---	---
		F	0	---	---	1	1.1	78.0	0	---	---	0	---	---
		M and F	0	---	---	1	0.6	78.0	1	0.6	94.0	0	---	---
IV	5 ppm	M	0	---	---	1	1.1	101.0	0	---	---	1	1.1	30.0
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	1	0.6	101.0	0	---	---	1	0.6	30.0
V	Controls in chambers	M	0	---	---	2	2.2	78.5	0	---	---	0	---	---
		F	0	---	---	1	1.1	63.0	0	---	---	1	1.1	78.0
		M and F	0	---	---	3	1.7	73.3	0	---	---	1	0.6	78.0
VI	Controls	M	0	---	---	2	2.2	110.0	0	---	---	0	---	---
		F	0	---	---	1	1.1	102.0	0	---	---	0	---	---
		M and F	0	---	---	3	1.7	107.3	0	---	---	0	---	---

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TABLE 9-49 (Continued)

			Animals with tumors											
			Encephalic tumors											
			Neuroblastomas			Other sites			Others				Totals[f]	
Group	Concentration	Sex	Total number	Percent[b]	Average latency time (wk)[d]	Total number	Percent[b]	Total number	Benign number	Malignant number	Number	Percent[b]	Number of different tumors/tumor-bearing animals	
I	250-150 ppm[e]	M	0	---	---	0	---	9	7	2	15	16.9	1.2	
		F	0	---	---	0	---	11	5	6	54	60.0	2.0	
		M and F	0	---	---	0	---	20	12	8	69	38.5	1.9	
II	50 ppm	M	0	---	---	1	1.1	14	14	0	20	22.2	1.6	
		F	0	---	---	1	1.1	6	3	3	56	62.2	1.7	
		M and F	0	---	---	2	1.1	20	17	3	76	42.2	1.7	
III	10 ppm	M	0	---	---	0	1.1	4	2	2	11	14.6	1.1	
		F	0	---	---	2	---	4	3	1	43	47.8	1.0	
		M and F	0	---	---	2	2.2	8	5	3	56	31.3	1.5	
IV	5 ppm	M	0	---	---	0	---	16	15	1	30	33.3	1.4	
		F	0	---	---	0	---	9	5	4	65	72.2	1.8	
		M and F	0	---	---	0	---	25	20	5	95	52.8	1.7	
V	Controls in chambers	M	0	---	---	1	1.1	8	7	1	17	18.9	1.1	
		F	0	---	---	1	1.1	4	2	2	38	42.2	1.4	
		M and F	0	---	---	2	1.1	12	9	3	55	30.6	1.7	
VI	Controls	M	0	---	---	0	---	7	7	0	14	15.6	1.1	
		F	0	---	---	3	3.3	8	5	3	56	62.2	1.7	
		M and F	0	---	---	3	1.7	15	12	3	70	38.9	1.6	

Exposure by inhalation to EDC in air at 250-150, 50 ppm, 10 ppm, and 5 ppm, 7 hr/day, 5 days wk, for 78 wk. Results after 148 wk (end of experiment).

[a] Sprague-Dawley rats, 12 wk old at start.

[b] The percentages refer to the corrected numbers.

[c] Average age at the onset of the first mammary tumor per animal detected at the periodic control or at autopsy.

[d] Average time from the start of the experiment to detection at the periodic control or at autopsy.

[e] After a few weeks the dose was reduced to 150 ppm, because of the high toxicity at the 250 ppm level.

[f] Several animals with 2 or more tumors.

TABLE 9-50. MAMMARY TUMORS IN SPRAGUE-DAWLEY RATS
EXPOSED TO EDC
(Maltoni et al. 1980)

		Animals			Mammary tumors			
Group	Concentration	Sex	Number at start	Corrected number[a]	Total number	Percent[b]	Average latency time (wk)[c]	Number of tumors/tumor-bearing animals
I	250-150 ppm[d]	M	90	89	11	12.3	92.9	1.1
		F	90	90	52	57.7	78.6	1.9
		M and F	180	179	63	35.2	81.1	1.7
II	50 ppm	M	90	90	10	11.1	88.8	1.4
		F	90	90	58	64.4	78.5	1.5
		M and F	180	180	68	37.8	80.0	1.5
III	10 ppm	M	90	89	5	5.6	60.8	1.0
		F	90	90	43	47.8	79.4	1.4
		M and F	180	179	48	26.8	77.5	1.4
IV	5 ppm	M	90	90	11	12.2	110.2	1.4
		F	90	90	65	72.2	83.2	1.6
		M and F	180	180	76	42.2	87.1	1.5
V	Controls in chambers	M	90	90	8	8.9	85.5	1.0
		F	90	90	38	42.2	83.3	1.8
		M and F	180	180	46	25.5	83.6	1.6
VI	Controls	M	90	90	5	5.5	92.0	1.0
		F	90	90	52	57.8	85.5	1.5
		M and F	180	180	57	31.7	86.1	1.5
	Total		1080	1078				

(continued on the following page)

TABLE 9-50 (Continued)

			Mammary tumors[e]											
					Histological evaluation									
					Mammary tumors			Zymbal gland carcinomas						
Group	Concentration	Sex	Total number	Percent[f]	Number	Percent[g]	Average latency time (wk)[c]	Number	Percent[g]	Average latency time (wk)[c]	Number	Percent[g]	Average latency time (wk)[c]	Number
I	250-150 ppm[d]	M	9	81.8	7	77.8	99.1	1	11.1	92.0	1	11.1	80.0	0
		F	50	96.1	47	94.0	81.3	8	16.0	71.5	3	6.0	99.3	0
		M and F	59	93.6	54	91.5	83.6	9	15.2	71.7	4	6.8	85.5	0
II	50 ppm	M	9	90.0	7	77.8	100.3	1	11.1	60.0	1	11.1	64.0	0
		F	53	91.4	49	92.4	80.7	9	17.0	73.8	1	1.9	88.0	0
		M and F	62	91.2	56	90.3	83.1	10	16.1	72.4	2	3.2	76.0	0
III	10 ppm	M	5	100.0	3	60.0	72.0	0	---	---	2	40.0	44.0	0
		F	38	88.4	33	86.8	80.9	8	21.0	88.5	0	---	---	0
		M and F	43	89.6	36	83.7	80.1	8	18.6	88.5	2	4.6	44.0	0
IV	5 ppm	M	11	100.0	11	100.0	110.2	0	---	---	1	9.1	134.0	0
		F	60	92.3	56	93.3	86.4	10	16.7	87.4	2	3.3	88.0	0
		M and F	71	93.4	67	94.6	90.3	10	14.1	87.4	3	4.2	101.3	0
V	Controls in chambers	M	8	100.0	7	87.5	85.1	0	---	---	1	14.3	88.0	0
		F	35	92.1	27	77.1	85.5	15	46.8	80.1	1	2.8	124.0	0
		M and F	43	93.5	34	79.1	85.6	15	38.5	80.1	2	4.6	106.0	0
VI	Controls	M	5	100.0	3	60.0	105.7	0	---	---	2	40.0	72.0	0
		F	49	94.2	47	95.9	88.1	8	16.3	80.4	0	---	---	2
		M and F	54	94.7	50	92.6	89.3	8	14.8	80.4	2	3.7	72.0	2

Group	Sex	Percent[g]	Average latency time (wk)[c]
I	M	---	---
	F	---	---
	M and F	---	---
II	M	---	---
	F	---	---
	M and F	---	---
III	M	---	---
	F	---	---
	M and F	---	---
IV	M	---	---
	F	---	---
	M and F	---	---
V	M	---	---
	F	---	---
	M and F	---	---
VI	M	---	---
	F	4.1	73.0
	M and F	3.7	73.0

Exposure by inhalation to EDC in air at 250-150 ppm, 150 ppm, 50 ppm, 10 ppm, and 5 ppm, 7 hr/day, for 78 wk. Results after 148 wk (end of experiment).

[a] Animals alive after 12 wk, when the first tumor (a mammary carcinoma) was observed.

[b] The percentages refer to the corrected numbers.

[c] Average age at the onset of first mammary tumor per animal, detected at the periodic control or at autopsy.

[d] After a few weeks the dose was reduced to 150 ppm, because of the high toxicity at the 250 ppm level.

[e] Two or more tumors of the same or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animal.

[f] The percentages refer to total number of animals bearing mammary tumors.

[g] The percentages refer to total number of animals bearing mammary tumors, histologically examined.

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chamber, but not significant when compared to controls outside of the chamber. Although the author stated that the onset of fibromas and fibroadenomas was age-correlated, the incidences of these tumors observed in the various groups were probably due instead to the differences in survival rates within the groups. The highest difference in incidence was found between the control groups in the chamber, which had low survival rates, and the groups treated with EDC at 5 ppm, which had high survival rates. The difference in survival rates is thus seen to be related to the differences in incidence in the two control groups.

9.5.1.5 Maltoni et al. (1980) Mouse Study--Four groups of Swiss mice (180 mice of both sexes per group) were exposed to EDC, at the level of purity previously described for the rat inhalation study, in concentrations of 250-150 ppm, 50 ppm, 10 ppm, and 5 ppm, respectively, 7 hours per day, 5 days per week, for 78 weeks. After several days of 250 ppm exposure, the mice began to exhibit severe toxic effects, and the concentration was reduced to 150 ppm. One group of 249 mice served as controls. The design of the experiment is given in Table 9-51.

At the end of the treatment period, the animals were allowed to live until spontaneous death. The remainder of the procedure was the same as that described previously for the Maltoni et al. (1980) rat study.

The survival rates for female mice were slightly lower in the group treated with EDC at 250-150 ppm. The survival rates for mice at 52 and 78 weeks of age are shown in Table 9-52. At 52 and 78 weeks, the overall survival rates were 82.4% and 45.9%, respectively. The survival rates after 52 weeks from the start of the experiment are also given in Table 9-52. The overall survival rate was 67.8%.

TABLE 9-51. DESIGN SUMMARY FOR 1,2-DICHLOROETHANE (EDC) EXPERIMENT IN SWISS MICE[a] (Maltoni et al. 1980)

Group	Concentration	Animals[b]	
		Sex	Number
I	250-150 ppm[c]	M	90
		F	90
II	50 ppm	M	90
		F	90
III	10 ppm	M	90
		F	90
IV	5 ppm	M	90
		F	90
V	Control	M	115
		F	134

[a] Exposed 7 hours/day, 5 days/week, for 78 weeks.

[b] Swiss mice, 11 weeks old at start.

[c] After a few weeks the dose was reduced to 150 ppm, because of high toxicity at the 250 ppm level.

The results of histopathologic analysis of various tumors are shown in Table 9-53 . These results do not indicate a statiscally significant increase in the incidence of any specific type of tumor in the treated mice as compared with controls.

In conclusion, although Maltoni et al. conducted extensive carcinogenicity studies in rats and mice, no significant incidences of tumors were seen in any of the target organs. Several factors may have contributed to these findings, such as differences in the strains of rats used, and dose levels that appear to have been less than maximally tolerated doses.

TABLE 9-52 . SURVIVAL OF SWISS MICE EXPOSED TO EDC AT 52 and 78 WEEKS[a]
(Maltoni et al. 1980)

Group	Dose (ppm)	Sex	Initial numbers	Survivors at 52 weeks of age		Survivors at 78 weeks of age		Survivors after 52 weeks from start of study	
				Number	Percent	Number	Percent	Number	Percent
I	250-150 ppm[b]	M	90	56	62.2	26	28.9	39	43.3
		F	90	75	83.3	44	48.9	58	64.4
II	50	M	90	68	75.6	30	33.3	46	51.1
		F	90	83	92.2	49	54.4	73	81.1
III	10	M	90	74	82.2	34	37.8	59	65.6
		F	90	86	95.6	50	55.6	72	80.0
IV	5	M	90	54	60.0	26	28.9	42	46.7
		F	90	84	93.3	68	75.6	84	93.3
V	Control	M	115	91	79.1	42	36.6	72	62.6
		F	134	127	94.8	76	56.8	112	83.6

[a] Mice were 11 weeks old at the start of the experiment.

[b] After a few weeks the dose was reduced to 150 ppm, because of high toxicity at the 250 ppm level.

TABLE 9-53 TUMOR INCIDENCE IN SWISS MICE EXPOSED TO DCM
(Maltoni et al. 1988)

					Animals with tumors								
			Animals[a]		Mammary tumors			Pulmonary adenomas			Leukemias		
Group	Concentration	Sex	Number at start	Corrected number[b]	Total number	Percent[c]	Average latency time (wk)[d]	Total number	Percent[c]	Average latency time (wk)[d]	Total number	Percent[c]	Average latency time (wk)[d]
I	250-150 ppm[e]	M	90	81	0	---	---	0	---	---	1	1.2	75.0
		F	90	84	5	6.0	69.0	1	3.6	85.7	1	1.2	63.0
		M and F	180	165	5	3.0	69.0	1	1.8	85.7	2	1.2	69.0
II	50 ppm	M	90	87	0	---	---	3	3.4	75.3	6	6.9	49.8
		F	90	87	3	3.4	76.0	2	2.3	74.5	4	4.6	59.2
		M and F	180	174	3	1.7	76.0	5	2.9	75.0	10	5.7	65.6
III	10 ppm	M	90	89	1	1.1	32.0	4	4.5	85.7	6	6.7	54.5
		F	90	88	6	6.8	75.7	2	2.3	53.5	5	5.7	69.6
		M and F	180	177	7	4.0	67.7	6	3.4	75.0	11	6.2	61.4
IV	5 ppm	M	90	69	0	---	---	1	1.4	66.0	2	2.9	79.0
		F	90	89	5	5.6	82.6	4	4.5	85.0	6	6.7	69.8
		M and F	180	158	5	3.2	82.6	5	3.2	76.8	8	5.1	72.1
V	Controls	M	115	111	0	---	---	4	3.6	78.5	6	5.4	65.8
		F	134	133	7	5.3	77.4	4	3.0	51.2	15	11.3	61.1
		M and F	249	244	7	2.9	77.4	8	3.3	64.9	21	8.6	62.6
Total			969	918									

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TABLE 9-53 (continued)

			Animals with tumors											
									Angiosarcomas					
			Nephroblastomas			Kidney adenocarcinomas			Liver			Other sites		
Group	Concentration	Sex	Total number	Percent^c	Average latency time (wk)^d	Total number	Percent^c	Average latency time (wk)^d	Total number	Percent^c	Average latency time (wk)^d	Total number	Percent^c	Average latency time (wk)^d
I	250-150 ppm^e	M	0	---	---	0	---	---	0	---	---	1	1.2	40.0
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	1	0.6	40.0
II	50 ppm	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
III	10 ppm	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
IV	5 ppm	M	0	---	---	0	---	---	0	---	---	0	---	125.0
		F	0	---	---	1	1.1	62.0	0	---	---	0	---	131.0
		M and F	0	---	---	1	0.6	62.0	0	---	---	0	---	128.0
V	Controls in chambers	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
VI	Controls	M	0	---	---	0	---	---	0	---	---	1	0.9	69.0
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	1	0.4	69.0

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TABLE 9-53 (continued)

			Animals with tumors											
			Angiomas and fibroangiomas											
			Liver			Other sites			Hepatomas			Forestomach epithelial tumors		
Group	Concentration	Sex	Total number	Percent^c	Average latency time (wk)^d	Total number	Percent^c	Average latency time (wk)^d	Total number	Percent^c	Average latency time (wk)^d	Total number	Percent^c	Average latency time (wk)^d
I	250-150 ppm^e	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
II	50 ppm	M	0	---	---	1	1.1	76.0	0	---	---	0	---	---
		F	1	1.1	83.0	1	1.1	83.0	0	---	---	0	---	---
		M and F	1	0.6	83.0	2	1.1	79.5	0	---	---	0	---	---
III	10 ppm	M	0	---	---	0	---	91.0	0	---	---	0	---	---
		F	0	---	---	1	1.1	91.0	0	---	---	0	---	---
		M and F	0	---	---	1	0.6	---	0	---	---	0	---	---
IV	5 ppm	M	0	---	---	0	---	---	0	---	---	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	---	---	0	---	---	0	---	---	0	---	---
V	Controls in chambers	M	0	0.9	69.0	1	0.9	76.0	4	3.5	82.0	0	---	---
		F	0	---	---	0	---	---	0	---	---	0	---	---
		M and F	0	0.4	69.0	1	0.4	76.0	4	1.6	82.0	0	---	---

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TABLE 9-53 (continued)

			Animals with tumors											
			Skin epithelial tumors			Subcutaneous sarcomas			Others			Total[f]		
Group	Concentration	Sex	Total number	Percent[c]	Average latency time (wk)[d]	Total number	Percent[c]	Average latency time (wk)[d]	Total number	Benign number	Malignant number	Number	Percent[c]	Number of different tumors/tumor-bearing animals
I	250-150 ppm[e]	M	0	---	---	0	---	---	0	0	0	2	2.4	1.0
		F	0	---	---	0	---	---	2	2	0	11	12.9	1.0
		M and F	0	---	---	0	---	---	2	2	0	13	7.7	1.0
II	50 ppm	M	0	---	---	0	---	---	1	0	1	9	10.6	1.7
		F	1	1.1	103.0	0	---	---	4	3	1	15	17.2	1.1
		M and F	1	0.6	103.0	0	---	---	5	3	2	24	14.0	1.2
III	10 ppm	M	0	---	---	1	1.1	77.0	1	1	0	12	13.5	1.1
		F	0	---	---	1	1.1	25.0	2	1	1	17	19.1	1.0
		M and F	0	---	---	2	1.1	51.0	3	2	1	29	16.3	1.1
IV	5 ppm	M	0	---	---	0	---	---	1	0	1	4	5.7	1.0
		F	1	1.1	79.0	0	---	---	4	3	1	19	21.3	1.0
		M and F	1	0.6	79.0	0	---	---	5	3	2	23	14.5	1.0
V	Controls in chambers	M	1	0.9	109.0	1	0.9	106.0	1	1	0	14	12.4	1.5
		F	1	0.7	77.0	0	---	---	4	2	2	27	20.1	1.1
		M and F	2	0.8	93.0	0	0.6	106.0	5	3	2	41	16.6	1.7

Exposure by inhalation to EDC in air at 250-150 ppm, 50 ppm, 10 ppm, and 5 ppm, 7 hr/day, 5 days/wk, for 78 wk.
Results after 119 weeks (end of experiment).

[a] Swiss mice, 11 wk old at start.

[b] Animals alive after 24 wk, when the first tumor (a leukemia) was observed.

[c] The percentages refer to the corrected numbers.

[d] Average time from the start of the experiment to detection at the periodic control or at autopsy.

[e] After a few weeks the dose was reduced to 150 ppm, because of high toxicity at the 250 ppm level.

[f] Several animals with two or more tumors.

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9.5.1.6 Theiss et al. (1977) Mouse Study--Theiss et al. (1977) conducted a pulmonary tumor bioassay with EDC and other organic contaminants of drinking water in the United States. The compounds were injected intraperitoneally into 6- to 8-week-old mice of the A/st strain. Each dose of reagent-grade EDC, with tricaprylin as the vehicle, was injected into mice in groups of 20, three times a week, for a total of 24 injections per mouse. Dose levels of 20, 40, and 100 mg/kg (the maximum tolerated dose) were used.

The mice were sacrificed 24 weeks after the first injection, and their lungs were placed in Tellyesniczky's fluid. After 48 hours, the lungs were examined microscopically for surface adenomas, and the frequency of lung tumors in each group was compared with that in a vehicle-treated control group by means of the Student's t Test. The incidence of lung tumors increased with dose, but none of the groups had pulmonary adenoma responses that were significantly greater ($P > 0.05$) than that of the vehicle-treated control mice (Table 9-54). Because they found a non-significant elevation in pulmonary tumor response, the authors suggested further investigation of the carcinogenic potential of EDC.

TABLE 9-54. PULMONARY TUMOR RESPONSE IN STRAIN A/st MICE INJECTED WITH EDC
(Theiss et al. 1977)

Dose/injection (mg/kg)	Number of injections	Fraction surviving	Number of tumors/mouse
0[a]	24	46/50 (92%)	0.39 ± 0.06
20	24	14/20 (70%)	0.21 ± 0.06
40	24	16/20 (80%)	0.44 ± 0.11
100	24	20/20 (100%)	0.75 ± 0.17

[a] Tricaprylin vehicle.

9.5.1.7 Van Duuren et al. (1979) Mouse Study--Van Duuren et al. (1979) conducted a bioassay of EDC and of a suspected metabolite, chloracetaldehyde, as initiators, promoters, and complete carcinogens using two-stage skin tests. Female non-inbred ICR/Ha Swiss mice were used, with treatment beginning at 6-8 weeks of age. The experimental group consisted of 30 animals, exclusive of the no-treatment groups or those receiving repeated application of phorbol myristate acetate (PMA). The results of this study are given in Table 9-55 . The compounds, in 0.1 ml and 0.2 ml acetone, were applied three times a week to the dorsal skin. Skin lesions were diagnosed as papillomas when they reached approximately 1 mm and persisted for 30 days or more.

All animals were examined daily and weighed monthly; findings were recorded monthly. Animals in poor health or with large tumor masses were killed. Animals were completely autopsied at the termination of the experiment or at death. Tissue sections were fixed in 10% formalin, processed, blocked in paraffin, and stained with hematoxylin and eosin for pathologic diagnosis. The results indicate that neither EDC nor chloroacetaldehyde induced a statistically significant increase in the incidence of carcinomas of the skin. This result was probably due to the low dose levels used in the study. EDC was found to induce a statistically significant increase in the incidence of benign lung papillomas.

In summary, the NCI study (1978), as well as the studies by Theiss et al. (1977) and Van Duuren et al. (1979), show that, under appropriate conditions, EDC can increase the incidence of tumors. The data obtained in mutagenicity studies have also shown that, under appropriate experimental conditions, EDC can cause DNA damage (Storer et al. 1982) and mutations (Guengerich et al. 1980). In contrast, the lifetime inhalation study conducted by Maltoni et al. (1980) showed no increased incidence of tumors.

TABLE 9-55. MOUSE SKIN BIOASSAY OF 1,2-DICHLOROETHANE AND CHLOROACETALDEHYDE
(adapted from Van Duuren et al. 1979)

	Initiation-promotion[a]			Repeated application[b]			
Compound	Dose mg/application/ mouse	Days to first tumor	Mice with papillomas[c]/ total papillomas	Dose mg/application/ mouse	Days to first tumor	Mice with papillomas[c]/ total papillomas	No. of mice with distant tumors[d]
1,2-Dichloroethane	126.0	357	3/3	126.0	---	0	26 lung P<0.0005 3 stomach
				42.0	---	0	17 lung 1 stomach
Chloroacetaldehyde	1.0	152	3/3 (1)	1.0	---	0	14 lung 1 stomach
PMA controls (120 mice)	0.0025	141	9/10 (1)	---	---	---	---
(90 mice)	0.0050	449	6/7 (2)	---	---	---	---
Acetone (0.1 ml)	---	---	---	0.1 ml	---	0	11 lung 2 stomach
No treatment (100 mice)	---	---	---	---	---	0	10 lung 5 stomach

[a] All applications were to the dorsal skin by micropipette. 1,2-dichloroethane was administered once only in 0.2 ml acetone, followed 14 days later by 5 ug of PMA in 0.2 ml acetone three times weekly. Chloroacetaldehyde was administered once only in 0.1 ml acetone, followed 14 days later by 2.5 ug of PMA in 0.1 ml acetone three times weekly.

[b] 1,2-dichloroethane was administered in 0.2 ml acetone. Chloroacetaldehyde was administered three times weekly in 0.1 ml acetone.

[c] Number of mice with squamous cell carcinomas are given in a parentheses.

[d] All lung tumors are benign papillomas; stomach tumors are papillomas of the forestomach and squamous cell carcinomas of the forestomach. P values are given only where significant, i.e., $P < 0.05$.

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The apparent discrepancies between inhalation and other routes of exposure in the oncogenicity studies have led to considerable discussion of the conduct and results of these studies (Maltoni et al. 1980, Hooper et al. 1980, Reitz et al. 1982). The NCI Clearing House Committee review of the NCI bioassay report (1978) acknowledged several design features which may have adversely affected the outcome of the experiment. For example, the studies were conducted in rooms housing animals dosed with other volatile carcinogens. It was concluded, however, that these shortcomings were not significant enough to invalidate the findings. Other investigators (Hooper et al. 1980) have concluded that unless unusual and unexpected synergisms occurred, the presence of other animals in the test rooms would not have affected the results.

Reitz et al. (1982) proposed that basic metabolism rate differences, specifically the saturation of the detoxification/excretion mechanism, occurred between the single gavage dose (and presumably other routes) and the longer-term inhalation dose. Their calculations suggest that EDC is metabolized by non-linear kinetics, and that the inhalation study did not produce peak blood levels sufficiently high to overcome the detoxification mechanism and produce a detectable incidence of tumors.

Regardless of the explanations for the observed differences (Hooper et al. 1980, Reitz et al. 1982), the data show both an ability of EDC to produce neoplasms and an inhalation level at which no tumors are formed. Thus, the results indicate the EDC is carcinogenic in rats and mice, and is a weak mutagen.

9.5.2 Epidemiologic Studies

No epidemiologic studies have been published regarding the carcinogenicity of EDC.

9.5.3 Quantitative Estimates

This quantitative section deals with estimation of the unit risk for EDC as a potential carcinogen in air and water, and with the potency of EDC relative to other carcinogens that have been evaluated by the CAG. The unit risk for an air or water pollutant is defined as the lifetime risk of cancer to humans from daily exposure to a concentration of 1 ug/m^3 of the pollutant in air by inhalation, or to a concentration of 1 ug/L in water by ingestion.

The unit risk estimate for EDC represents an extrapolation below the dose range of experimental data. There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at the extremely low concentrations, including the unit concentration given above, that must be dealt with in evaluating environmental hazards. For practical reasons the correspondingly low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. Low-dose extrapolation must, therefore, be based on current understanding of the mechanisms of carcinogenesis. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is based in part on the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal response that is characteristic of mutagenesis is associated with a linear (at low doses) non-threshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear non-threshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin). Linearity is also supported when the mode of action of the carcinogen in question is similar to that of the background cancer production in the exposed population.

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the non-threshold model, which is linear at low doses, has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. Any risk estimates made with such a model should be regarded as conservative, representing the plausible upper limit for the risk; i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

The unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. This is true for several reasons. First, there are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans as compared to animals, based on a ratio of weight to surface area, is virtually without experimental verification as regards carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative carcinogenic potency of a given agent, as compared with that of other carcinogens. Such estimates are, of course, more reliable when the comparisons are based on studies in which the test species, strain, sex, and routes of exposure are similar.

The quantitative aspect of carcinogen risk assessment is addressed here because of its possible value in the regulatory decision-making process, e.g., in setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, the imprecision of presently available technology for estimating cancer risks to humans at low levels of exposure should be recognized. At best, the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk--that is, with this model it is not likely that the true risk would be much more than the estimated risk, but it could be considerably lower. The risk estimates presented in subsequent sections should not be regarded, therefore, as accurate representations of the true cancer risks even when the exposures involved are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-risk limits is found to be useful.

9.5.3.1 Procedures for the Determination of Unit Risk--

9.5.3.1.1 Low-dose extrapolation model. The mathematical formulation chosen to describe the linear non-threshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment.

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d + q_1 d^2 + \ldots + q_k d^k)\right]$$

where

$$q_i \geq 0, \ i = 0, 1, 2, \ldots, k$$

Equivalently,

$$P_t(d) = 1 - \exp\left[-(q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where

$$P_t(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d.

The point estimate of the coefficients q_i, $i = 0, 1, 2, \ldots, k$, and consequently, the extra risk function, $P_t(d)$, at any given dose d, is calculated by maximizing the likelihood function of the data.

The point estimate and the 95% upper confidence limit of the extra risk, $P_t(d)$, are calculated by using the computer program, GLOBAL79, developed by Crump and Watson (1979). At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^*, on parameter q_1. Whenever $q_1 > 0$, at low doses the extra risk $P_t(d)$ has approximately the form $P_t(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95% upper confidence limit on the extra risk and R/q_1^* is a 95% lower confidence limit on the dose, producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function.

The upper-limit q_1^* is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2\,(L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper-limit (one-sided). This approach of computing the upper confidence limit for the extra risk $P_t(d)$ is an improvement on the Crump et al. (1977) model. The upper confidence limit for the extra risk calculated at low doses is alway linear. This is conceptually consistent with the linear nonthreshold concept discussed earlier. The slope, q_1^*, is taken as an upper bound of the potency of the chemical in inducing cancer at low doses. (In the section calculating the risk estimates, $P_t(d)$ will be abbreviated as P.)

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment, including the control group.

Whenever the multistage model does not fit the data sufficiently well, data at the highest dose is deleted and the model is refit to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$X^2 = \sum_{i=1}^{h} \frac{(X_i - N_iP_i)^2}{N_iP_i\,(1-P_i)}$$

is calculated where N_i is the number of animals in the i^{th} dose group, X_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unaccepatable whenever X^2 is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficents.

9.5.3.1.2 Selection of data. For some chemicals, several studies in different animal species, strains, and sexes, each run at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies to use in the model. It may also be appropriate to correct for metabolism differences between species and for absorption factors via different routes of administration. The procedures used in evaluating these data are consistent with the approach of making a maximum-likely risk estimate. They are as follows:

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the set of data having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers $A_1, A_2, \ldots, A_m$ is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

9.5.3.1.3 Calculation of human equivalent dosages. Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner.

Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e), and

W = average weight of the experimental animal

The lifetime exposure is then

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

9.5.3.1.3.1 Oral. Often exposures are not given in units of mg/day, and it becomes necessary to convert the given exposures into mg/day. Similarly, in drinking water studies, exposure is expressed as ppm in the water. For example, in most feeding studies exposure is given in terms of ppm in the diet. In these cases, the exposure in mg/day is

$$m = \text{ppm} \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet or water, F is the weight of the food or water consumed per day in kg, and r is the absorption fraction. In the absence of any data to the contrary, r is assumed to be equal to one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area, or two-thirds power of the weight. Water demands are also assumed to be proportional to the surface area, so that

$$m \propto \text{ppm} \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto \text{ppm}$$

As a result, ppm in the diet or water is often assumed to be an equivalent exposure between species. However, this is not justified for the present study, since the ratio of calories to food weight is very different in the diet of man as compared to laboratory animals, primarily due to differences in the moisture content of the foods eaten. For the same reason, the amount of drinking water required by each species also differs. It is therefore necessary to use an empirically derived factor, $f = F/W$, which is the fraction of an organism's body weight that is consumed per day as food, expressed as follows:

		Fraction of body weight consumed as	
Species	W	f_{food}	f_{water}
Man	70	0.028	0.029
Rats	0.35	0.05	0.078
Mice	0.03	0.13	0.17

Thus, when the exposure is given as a certain dietary or water concentration in ppm, the exposure in mg/$W^{2/3}$ is

$$\frac{m}{rW^{2/3}} = \frac{ppm \times F}{W^{2/3}} = \frac{ppm \times f \times W}{W^{2/3}} = ppm \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day = $m/Wr = s$, the conversion is simply

$$\frac{m}{rW^{2/3}} = s \times W^{1/3}$$

9.5.3.1.3.2 Inhalation. When exposure is via inhalation, the calculation of dose can be considered for two cases where 1) the carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed proportionally to the amount of air breathed in, and 2) where the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to the metabolic rate, which in turn is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

9.5.3.1.3.2.1 Case 1--Agents that are in the form of particulate matter or virtually completely absorbed gases, such as sulfur dioxide, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day may be expressed as

$$m = I \times v \times r$$

where I = inhalation rate per day in m^3, v = mg/m^3 of the agent in air, and r = the absorption fraction.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (FASEB 1974) that 25 g mice breathe 34.5 liters/day and 113 g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\,(W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\,(W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 30 m^3/day* is adopted as a standard breathing rate (International Commission on Radiological Protection 1977). The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, $i = I/W$, based upon the previously stated relationships, are tabulated as follows:

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

---

*From "Recommendation of the International Commission on Radiological Protection," page 9. The average breathing rate is 10^7 cm^3 per 8-hour workday and 2×10^7 cm^3 in 24 hours.

Therefore, for particulates or completely absorbed gases, the equivalent exposure in mg/$W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species.

9.5.3.1.3.2.2 Case 2--The dose in mg/day of partially soluble vapors is proportional to the O_2 consumption, which in turn is proportional to $W^{2/3}$ and is also proportional to the solubility of the gas in body fluids, which can be expressed as an absorption coefficient, r, for the gas. Therefore, expressing the O_2 consumption as $O_2 = k\ W^{2/3}$, where k is a constant independent of species, it follows that

$$m = k\ W^{2/3} \times v \times r$$

or

$$d = \frac{m}{W^{2/3}} = kvr$$

As with Case 1, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction, r, is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or ug/m^3 in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given "stage" of anesthesia is similar in man and animals (Dripps et al. 1977). When the animals are exposed via the oral route and human exposure is via inhalation or vice versa, the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

9.5.3.1.4 Calculation of the unit risk from animal studies. The risk associated with d mg/kg$^{2/3}$/day is obtained from GLOBAL79 and, for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of $X = 1$. This value is estimated simply by finding the number of mg/kg$^{2/3}$/day that corresponds to one unit of X, and substituting this value into the above relationship. Thus, for example, if X is in units of ug/m^3 in the air, then for case 1, $d = 0.29 \times 70^{1/3} \times 10^{-3}$ mg/kg$^{2/3}$/day, and for case 2, $d = 1$, when ug/m^3 is the unit used to compute parameters in animal experiments.

If exposures are given in terms of ppm in air, the following calculation may be used:

$$1 \text{ ppm} = 1.2 \times \frac{\text{molecular weight (gas)}}{\text{molecular weight (air)}} \text{ mg/m}^3$$

Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures, and then to increase the j^{th} polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k$$

and to use mg/kg equivalents for the unit risk values.

9.5.3.1.4.1 Adjustment for less than the natural lifetime of an experiment. If the duration of experiment L_e is less than the natural lifespan of the test animal L, the slope q_1^*, or more generally the exponent $g(d)$, is increased by multiplying a factor $(L/L_e)^3$. We assume that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the third power of the age, and often by a considerably higher power, as demonstrated by Doll (1971). Thus, it is expected that the cumulative tumor rate would increase by at least the third power of age. Using this fact, it is assumed that the slope q_1^*, or more generally the exponent $g(d)$, would also increase by at least the third power of age. As a result, if the slope q_1^* [or $g(d)$] is calculated at age L_e, it is expected that if the experiment had been continued for the full lifespan L at the given average exposure, the slope q_1^* [or $g(d)$] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Daffer et al. (1980), where the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp\,[-f(t) \times g(d)]$$

9.5.3.2 Unit Risk Estimates--

9.5.3.2.1 Data available for potency calculation. The carcinogenic potency of EDC can only be estimated from animal data, since no human epidemiologic studies are available at the present time. EDC was shown to be carcinogenic in both rats and mice in a gavage study by the National Cancer Institute (NCI 1978). The only available inhalation study (Maltoni et al. 1980) did not indicate any significant carcinogenic effects in either rats or mice. The reason for this nonresponsiveness by inhalation is not known. In their evaluation of inhalation and gavage studies on EDC, Hooper et al. (1980) concluded that the discrepant results between the two exposure routes might be ascribed to one or more of the following causes:

(1) The strains of test animals differ in responsiveness;

(2) The route of exposure does make a difference concerning the carcinogenic action of EDC; or

(3) An artifact has been introduced by the intercurrent mortality.

Two approaches have been used herein to estimate the cancer risk from inhalation of EDC: direct estimation based on the results of the EDC gavage study, and indirect estimation based on the results of ethylene dibromide (EDB) inhalation and gavage studies.

The multistage model is used in connection with the most sensitive tumor sites, and for purposes of comparison, other extrapolation models and data sets are also used to estimate the carcinogenic potency of EDC.

Data from both rats and mice (NCI 1978) are used to estimate the carcinogenic potency of EDC. For rats, hemangiosarcomas in the circulatory system of male rats were selected, because these tumors are the most sensitive and were not located at the site of direct contact with the agent. Because of the high mortality rate in the high-dose group, the cancer risk is calculated by using two types of data:

1. Dichotomous data. The number of animals that survived at least 50 weeks was used as the denominator of the incidence rate (see Table 9-56.
2. Time-to-death data (see Table B-1, Appendix B).

For mice, hepatocellular carcinomas in male mice (Table 9-57) were used. Again, this tumor site was selected because it is the most sensitive in mice.

9.5.3.2.2 Choice of low-dose extrapolation models. In addition to the multistage model currently used by the CAG for low-dose extrapolation, three more models, the probit, the Weibull, and the one-hit, are also employed for purposes of comparison. These models cover almost the entire spectrum of risk estimates that could be generated from existing mathematical extrapolation

TABLE 9-56 INCIDENCE RATES OF HEMANGIOSARCOMAS IN THE CIRCULATORY SYSTEMS OF MALE OSBORNE-MENDEL RATS (NCI 1978)

Human (animal) dose (mg/kg/day)[a]	Incidence rates
0	0/40
4.85 (47)	9/48
9.80 (95)	7/27

---

[a] Human equivalent dose is calculated by d x (5/7) x (78/104) x $(0.5/70)^{1/3}$ = 0.103 x d, where d is the experimental dose in mg/kg/day, administered 5 days per week for 78 weeks. The lifespan for rats is assumed to be 104 weeks. The body weights are assumed to be 0.5 kg for rats and 70 kg for humans. This dose conversion assumes that the doses in mg per surface area are equivalent between species. For comparison, the risk is also calculated under the assumption that doses in mg/kg/day (i.e., without surface correction) are equivalent between species.

TABLE 9-57. INCIDENCE RATES OF HEPATOCELLULAR CARCINOMAS IN MALE B6C3F1 MICE (NCI 1978)

Human (animal) dose (mg/kg/day)[a]	Incidence rates
0	1/19
4.76 (97)	6/47
9.57 (195)	12/48

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[a] Human equivalent dose is calculated by d x (5/7) x (78/90) x $(0.035/70)^{1/3}$ = 4.91 x 10^{-2} x d, where d is the animal dose in mg/kg/day, administered 5 days per week for 78 weeks. The lifespan for mice is assumed to be 90 weeks. The body weights are 0.035 kg for male mice and 70 kg for humans. For comparison, the risk is also calculated under the assumption that doses in mg/kg/day (i.e., without surface correction) are equivalent between species.

models. Generally statistical in character, these models are not derived from biological arguments, except for the multistage model, which has been used to support the somatic mutation hypothesis of carcinogenesis (Armitage and Doll 1954, Wittemore 1978, Whittemore and Keller 1978). The main difference among these models is the rate at which the response function P(d) approaches zero or P(0) as dose d decreases. For instance, the probit model would usually predict a smaller risk at low doses that the multistage model because of the difference of the decreasing rate in the low-dose region. However, it should be noted that one could always artificially give the multistage model the same (or even greater) rate of decrease as the probit model by making some dose transformation and/or by assuming that some of the parameters in the multistage model are zero. This, of course, is not reasonable without knowing, a priori, what the carcinogenic process for the agent is. Although the multistage model appears to be the most reasonable or at least the most general model to use, the point estimate generated from this model is of limited value because it does not help to determine the shape of the dose-response curve beyond experimental exposure levels. Furthermore, point estimates at low doses extrapolated beyond the experimental doses could be extremely unstable and could differ drastically, depending on the amount of the lowest experimental dose. Since upper-bound estimates from the multistage model at low doses are relatively more stable than point estimates, it is suggested that the upper-bound estimate for the risk (or the lower-bound estimates for the dose) be used in evaluating the carcinogenic potency of a suspect carcinogen. The upper-bound estimate can be taken as a plausible estimate if the true dose-response curve is actually linear at low doses. The upper-bound estimate means that the risks are not likely to be higher, but could be lower if the compound has a concave upward dose-response curve or a threshold at low doses. Another reason one can, at best, obtain an upper-bound estimate of the risk when animal data are used is that the estimated risk is a probability conditional to the assumption that an animal carcinogen is also a human carcinogen. Therefore, in reality, the actual risk could range from a value near zero to an upper-bound estimate.

9.5.3.2.3 Calculation of the carcinogenic potency of EDC. Using the incidence data in Tables 9-56 and 9-57 and the corresponding human equivalent doses, with and without body surface correction, the maximum likelihood estimates of the parameters in each of four extrapolation models are calculated and presented in Table A-1 of Appendix A. These models can be used to calculate point estimates of risk at given doses or at doses for given levels of risk. The upper-bound estimates of the risk at 1 mg/kg/day, calculated by various models using different data sets, are presented in Table 9-58. From this table, it is observed that the multistage model predicts a comparable risk on the basis of either hemangiosarcomas in male rats or liver carcinomas in male mice, while the probit and Weibull models are extremely unstable and predict a wide range of risk, depending on the data base used. Figures 9-12 and 9-13 compare the maximum likelihood estimates of the four models over the relatively low dose range.

For the reasons discussed previously, the CAG recommends that the estimate $q_1^* = 6.9 \times 10^{-2}$ mg/kg/day be used to represent the carcinogenic potency of EDC by oral exposure. This value is calculated on the basis of hemangiosarcomas in male rats using the multistage model with the time factor. This value will also be used to estimate the risk of EDC by inhalation.

TABLE 9-58. UPPER-BOUND ESTIMATE OF RISK AT 1 MG/KG/DAY

Data base	Multistage (with time factor)	Probit	Weibull	One-hit
Hemangiosarcomas, dose with surface correction	5.4×10^{-2} (6.9×10^{-2})	0.29	0.28	5.4×10^{-2}
Hemangiosarcomas, dose without surface correction	7.0×10^{-3} (1.3×10^{-2})	0.17	0.19	7.0×10^{-3}
Hepatocellular carcinomas, dose with surface correction	3.8×10^{-2}	2.4×10^{-2}	4.3×10^{-2}	3.8×10^{-2}
Hepatocellular carcinomas, dose without surface correction	3.0×10^{-3}	1.1×10^{-5}	1.9×10^{-3}	3.0×10^{-3}

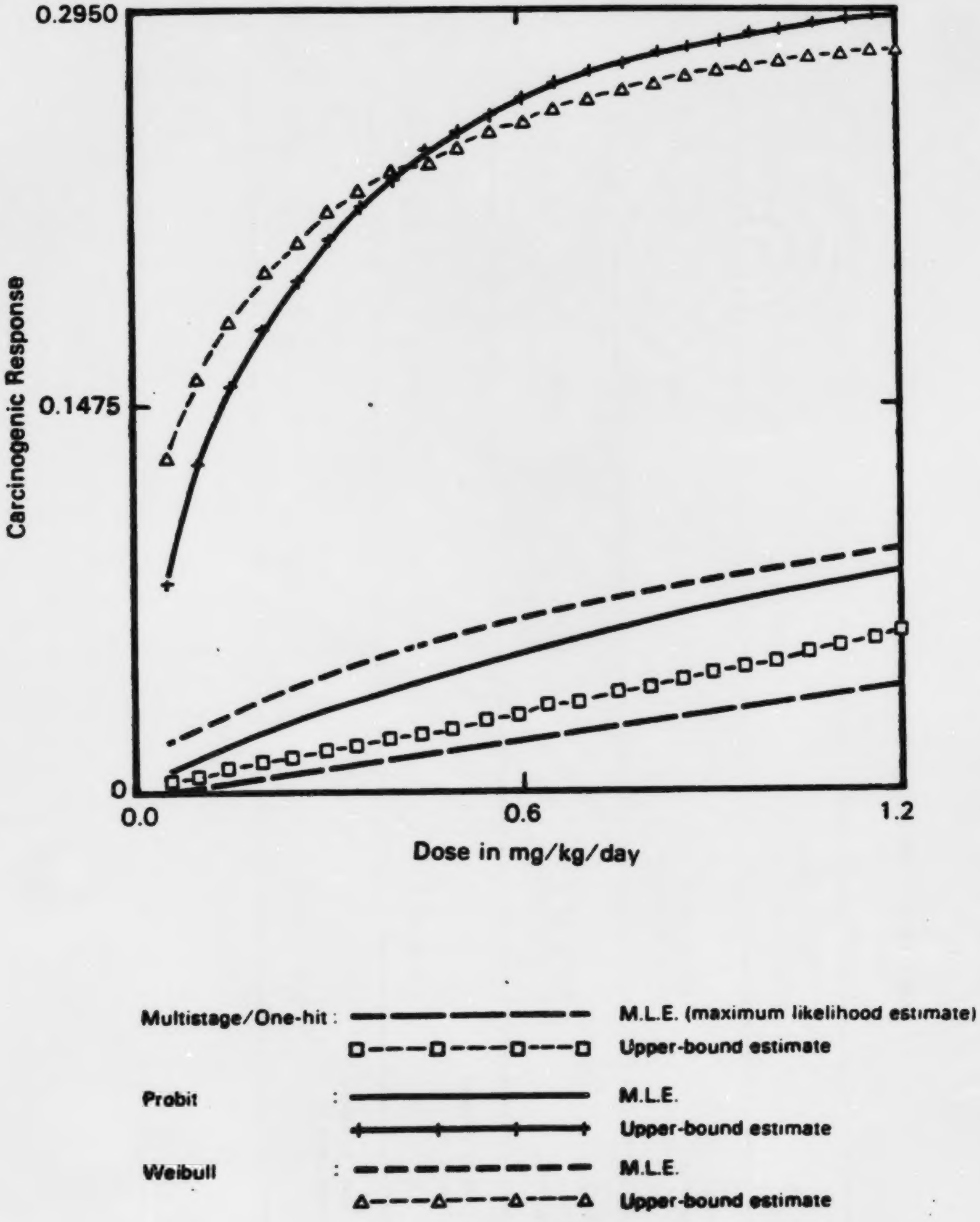

FIGURE 9-12 Point and upper-bound estimates of four dose-response models over low-dose region on the basis of hemangiosarcomas in rats; dose with surface correction. (NCI 1978)

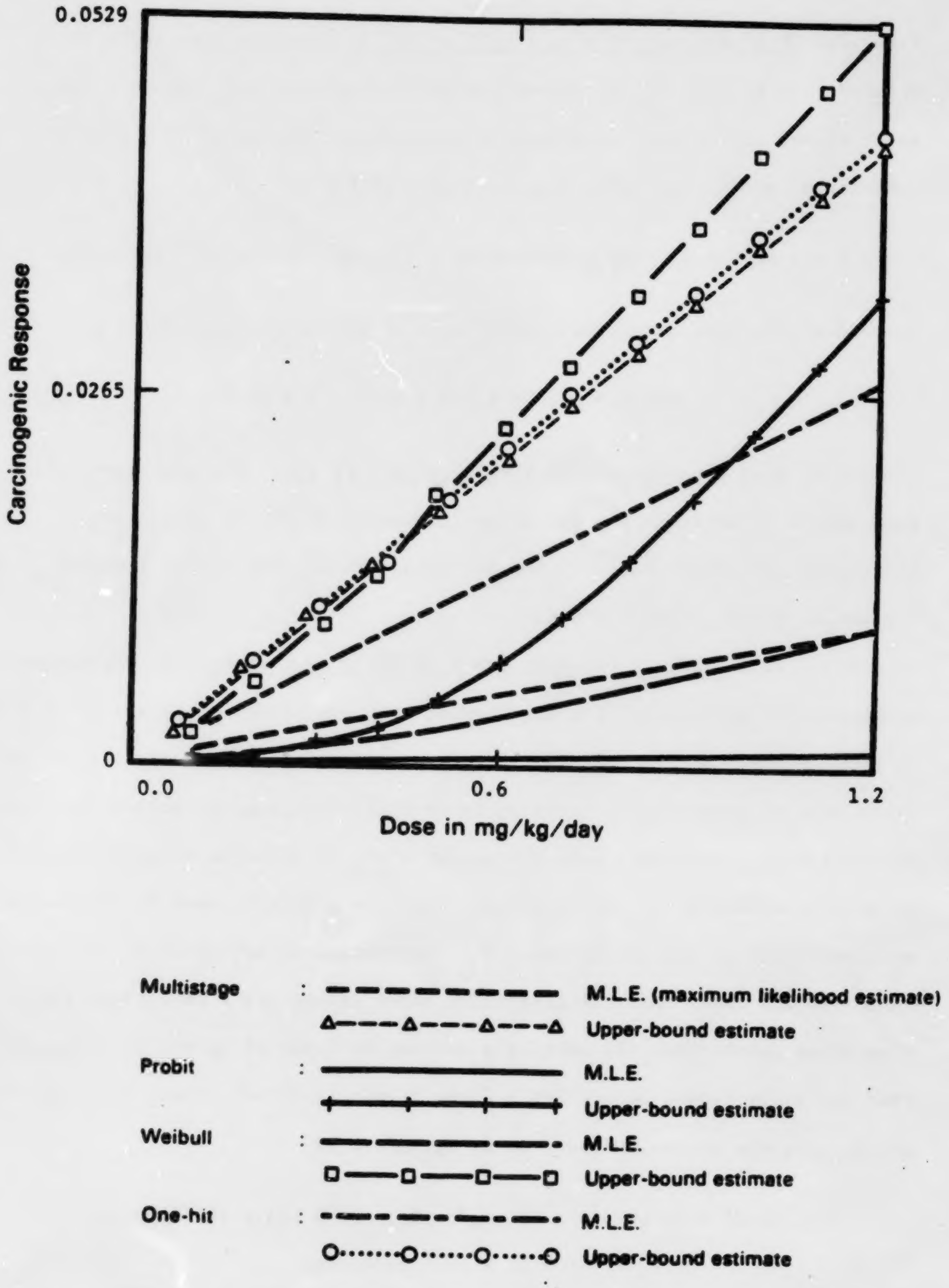

FIGURE 9-13 Point and upper-bound estimates of four dose-response models over low-dose region on the basis of liver carcinomas in mice; dose with surface correction. (NCI 1978)

9.5.3.2.4 Risk associated with 1 ug/L of EDC in drinking water. It is assumed that 100% of EDC in drinking water can be absorbed, and that the water intake is 2 L/day. Under these assumptions, the daily dose from consumption of water containing 1 ug/L (1 ppb) of EDC is

$$d = 1 \text{ ug/L} \times 2 \text{ L/day} \times 10^{-3} \text{ mg/ug} \times 1/70 \text{ kg} = 2.9 \times 10^{-5} \text{ mg/kg/day}$$

Therefore, the risk associated with 1 ug/L of EDC in drinking water is

$$P = 6.9 \times 10^{-2} \times 2.9 \times 10^{-5} = 2 \times 10^{-6}$$

9.5.3.2.5 Risk associated with 1 ug/m^3 of EDC in air. Two approaches are used herein to estimate the carcinogenic potency of EDC by inhalation: (1) direct estimation based on the EDC gavage study, and (2) an indirect estimation based on EDB studies.

9.5.3.2.5.1 Direct estimate based on EDC gavage study. It was estimated in the previous section that the carcinogenic potency of EDC by gavage is $q_1^* = 6.9 \times 10^{-2}$ mg/kg/day. If the relative absorption rate of EDC by inhalation and gavage in animals is known, it is possible to estimate carcinogenic potency by inhalation if the potency calculated from the gavage study is adjusted proportionately. As an approximation, it can be assumed that the effective dose by inhalation is only one-third of that by gavage. This assumption is motivated by the observation (Reitz et al. 1982) that DNA alkylation after gavage was 2 to 5 times higher than after inhalation. To calculate potency in terms of ug/m^3, it is assumed that the daily intake of air for a 70-kg person is 20 m^3. Thus, for 1 ug/m^3 of EDC in air, the corresponding dose in mg/kg/day is

$$(1/3) \times (1 \text{ ug/m}^3) \times (20 \text{ mg/day}) \times (1/70 \text{ kg}) \times (10^{-3} \text{ mg/ug})$$
$$= 9.52 \times 10^{-5} \text{ mg/kg/day}$$

On the basis of the above calculations, the carcinogenic potency of EDC by inhalation is estimated as follows:

$$q_1^* = (6.90 \times 10^{-2}) \times (9.52 \times 10^{-5}) = 6.6 \times 10^{-6}\ \text{ug/m}^3.$$

9.5.3.2.5.2 Indirect estimate based on EDB studies. The carcinogenic potency of EDC by inhalation can be estimated by utilizing the following assumption:

$$\frac{P(\text{EDC, I})}{P(\text{EDB, I})} = \frac{P(\text{EDC, G})}{P(\text{EDB, G})}$$

where P(EDC, I) and P(EDC, G) indicate the potencies of EDC by inhalation and by gavage, respectively, and P(EDB, I) and P(EDB, G) indicate the potency of EDC by inhalation and by gavage, respectively.

The potencies for EDC and EDB by gavage are estimated from the hemangiosarcomas in male rats in the NCI studies on EDC (NCI 1978) and EDB (NCI 1979). On the basis of gavage studies, it is estimated that EDB is approximately 10 times more potent than EDC. The estimation and the data used for calculating the EDB potency by gavage are presented in Appendix C.

The potency of EDB by inhalation is calculated as P(EDB, I) = 6.77×10^{-5} ug/m^3, on the basis of nasal cavity tumors in male rats (NCI 1979). The calculation and data are presented in Appendix C. On this basis, the potency of EDC by inhalation is calculated as follows:

$$P(\text{EDC,I}) = \frac{P(\text{EDC, G})}{P(\text{EDB, G})} \times P(\text{EDB, I})$$

$$= \frac{1}{10} \times 6.77 \times 10^{-5}$$

$$= 6.8 \times 10^{-6}\ \text{ug/m}^3$$

Practically no difference exists between this estimate and that calculated directly from the EDC gavage study data.

9.5.3.3 Comparison of Potency with Other Compounds--One of the uses of quantitative potency estimates is to compare the relative potencies of carcinogens. Figure 9-14is a histogram representing the frequency distribution of potency indices of 53 suspect carcinogens evaluated by the CAG. The data summarized by the histogram are presented in Table 9-59. The potency index is derived from q_1^*, the 95% upper bound of the linear component in the multistage model, and is expressed in term of $(\text{mMol/kg/day})^{-1}$. Where human data were available for an agent, they have been used to calculate the index. Where no human data were available, animal oral studies have been used in preference to animal inhalation studies, since oral studies constitute the majority of animal studies.

Based on available data concerning hemangiosarcomas in male rats (NCI 1978), the potency index for EDC has been calculated as 7×10^0. This figure is derived by multiplying the slope $q_1^* = 6.9 \times 10^{-2}$ mg/kg/day and the molecular weight of EDC, 98.9. This places the potency index for EDC in the fourth quartile of the 53 suspect carcinogens evaluated by the CAG.

The ranking of relative potency indices is subject to the uncertainties involved in comparing a number of potency estimates for different chemicals based on varying routes of exposure in different species, by means of data from studies whose quality varies widely. All of the indices presented are based on estimates of low-dose risk, using linear extrapolation from the observational range. These indices may not be appropriate for the comparison of potencies if linearity does not exist at the low-dose range, or if

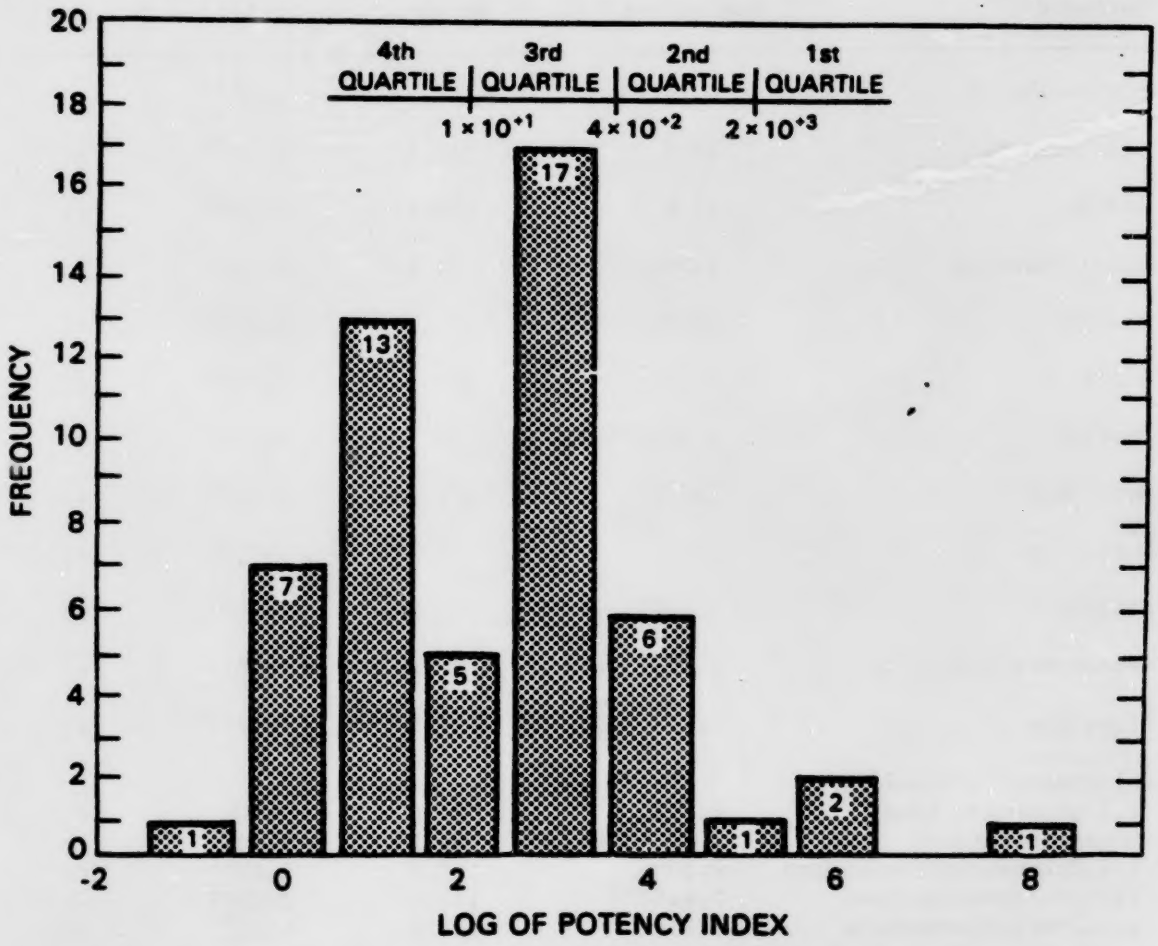

Figure 9-16 Histogram representing the frequency distribution of the potency indices of 53 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 9-59. RELATIVE CARCINOGENIC POTENCIES AMONG 53 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS[1,2,3]

Compound	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Acrylonitrile	0.24(W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	2924	312.3	$9x10^{+5}$	+6
Aldrin	11.4	369.4	$4x10^{+3}$	+4
Allyl chloride	$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	15(H)	149.8	$2x10^{+3}$	+3
B[a]P	11.5	252.3	$3x10^{+3}$	+3
Benzene	$5.2x10^{-2}$(W)	78	$4x10^{0}$	+1
Benzidene	234(W)	184.2	$4x10^{+4}$	+5
Beryllium	1.40	9	$1x10^{+1}$	+1
Cadmium	6.65(W)	112.4	$7x10^{+2}$	+3
Carbon tetrachloride	$1.30x10^{-1}$	153.8	$2x10^{+1}$	+1
Chlordane	1.61	409.8	$7x10^{+2}$	+3
Chlorinated ethanes				
1,2-dichloroethane	$6.9x10^{-2}$	98.9	$7x10^{0}$	+1
hexachloroethane	$1.42x10^{-2}$	236.7	$3x10^{0}$	0
1,1,2,2-tetrachloroethane	0.20	167.9	$3x10^{+1}$	+1
1,1,1-trichloroethane	$1.6x10^{-3}$	133.4	$2x10^{-1}$	-1
1,1,2-trichloroethane	$5.73x10^{-2}$	133.4	$8x10^{0}$	+1
Chloroform	$7x10^{-2}$	119.4	$8x10^{0}$	+1
Chromium	41(W)	100	$4x10^{+3}$	+4
DDT	8.42	354.5	$3x10^{+3}$	+3
Dichlorobenzidine	1.69	253.1	$4x10^{+2}$	+3
1,1-dichloroethylene	$1.47x10^{-1}$(I)	97	$1x10^{+1}$	+1
Dieldrin	30.4	380.9	$1x10^{+4}$	+4

(continued on the following page)

TABLE 9-59 (cont.)

Compound	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude (log$_{10}$ index)
Dinitrotoluene	0.31	182	$6x10^{+1}$	+2
Diphenylhydrazine	0.77	180	$1x10^{+2}$	+2
Epichlorohydrin	$9.9x10^{-3}$	92.5	$9x10^{-1}$	0
Bis(2-chloroethyl)ether	1.14	143	$2x10^{+2}$	+2
Bis(chloromethyl)ether	9300(I)	115	$1x10^{+6}$	+6
Ethylene dibromide (EDB)	8.51	187.9	$2x10^{+3}$	+3
Ethylene Oxide	0.63(I)	44.0	$3x10^{+1}$	+1
Heptachlor	3.37	373.3	$1x10^{+3}$	+3
Hexachlorobenzene	1.67	284.4	$5x10^{+2}$	+3
Hexachlorobutadiene	$7.75x10^{-2}$	261	$2x10^{+1}$	+1
Hexachlorocyclohexane				
technical grade	4.75	290.9	$1x10^{+3}$	+3
alpha isomer	11.12	290.9	$3x10^{+3}$	+3
beta isomer	1.84	290.9	$5x10^{+2}$	+3
gamma isomer	1.33	290.9	$4x10^{+2}$	+3
Methylene chloride	$6.3x10^{-4}$	84.9	$5x10^{-2}$	-1
Nickel	1.15(W)	58.7	$7x10^{+1}$	+2
Nitrosamines				
Dimethylnitrosamine	25.9(not by q_1^*)	74.1	$2x10^{+3}$	+3
Diethylnitrosamine	43.5(not by q_1^*)	102.1	$4x10^{+3}$	+4
Dibutylnitrosamine	5.43	158.2	$9x10^{+2}$	+3
N-nitrosopyrrolidine	2.13	100.2	$2x10^{+2}$	+2
N-nitroso-N-ethylurea	32.9	117.1	$4x10^{+3}$	+4
N-nitroso-N-methylurea	302.6	103.1	$3x10^{+4}$	+4
N-nitroso-diphenylamine	$4.92x10^{-3}$	198	$1x10^{0}$	0
PCBs	4.34	324	$1x10^{+3}$	+3

TABLE 9-59 . (continued)

Compound	Slope $(mg/kg/day)^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Phenols				
2,4,6-trichlorophenol	1.99×10^{-2}	197.4	4×10^{0}	+1
Tetrachlorodioxin	4.25×10^{5}	322	$1 \times 10^{+8}$	+8
Tetrachloroethylene	3.5×10^{-2}	165.8	6×10^{0}	+1
Toxaphene	1.13	414	$5 \times 10^{+2}$	+3
Trichloroethylene	1.9×10^{-2}	131.4	2.5×10^{0}	0
Vinyl chloride	1.75×10^{-2}(I)	62.5	1×10^{0}	0

Remarks:

1. Animal slopes are 95% upper-limit slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear non-threshold model.

2. The potency index is a rounded-off slope in $(mMol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by the molecular weight of the compound.

3. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

comparison is to be made at the high-dose range. If the latter is the case, then an index other than the one calculated above may be more appropriate.

9.5.4 Summary

9.5.4.1 Qualitative--Although several cancer bioassay studies of EDC have been reported, only the NCI bioassay in which EDC was administered to rats and mice by gavage produced a clear positive tumorigenic response.

In the NCI (1978) rat study, EDC produced a statistically significant increase in the incidence of squamous cell carcinomas of the forestomach, hemangiosarcomas of the circulatory system, and fibromas of subcutaneous tissue in male rats. There was also a statistically significant increased incidence of adenocarcinomas of the mammary gland and hemangiosarcomas of the circulatory system in female rats.

In the NCI (1978) studies in mice, EDC produced a statistically significant increased incidence of hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice and a statistically significant increased incidence of alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice.

Two inhalation studies of EDC were conducted. The study by Spencer et al. (1951) in Wistar rats showed no evidence of a postive response. However, this study was inadequate to assess the carcinogenicity of EDC because the experiment was conducted in a small number of animals for 212 days with 151 exposure days at 200 ppm. A second study by Maltoni et al. (1980), conducted in both rats and mice, did not produce a statistically significant increase in tumor incidences in any organ sites as compared to control animals.

The study by Theiss et al. (1977), a pulmonary bioassay in which EDC was administered intraperitoneally to strain A mice, produced a statistically insignificant increase in the incidence of lung tumors in treated animals.

In a study by Van Duuren et al. (1979), EDC was applied to the skin of ICR/Ha mice to assess its carcinogenic potential as a skin tumorigen. This study did not show a statistically significant increase in skin carcinomas; a significantly increased incidence of benign lung tumors in mice treated with the high dose (126/mg/mouse) was reported.

No case reports or epidemiologic studies concerning EDC were available in the published literature.

9.5.4.2 Quantitative--Data from studies using both rats and mice were used to estimate the carcinogenic potency of EDC. For rats, data on hemangiosarcomas in the circulatory system were used. For mice, data on hepatocellular carcinomas were used. The carcinogenic potencies estimated on the basis of these two data sets are comparable when the linearized multistage model is used. The upper-bound estimate of EDC potency is $q_1^* = 7 \times 10^{-2}$ mg/kg/day, calculated on the basis of hemangiosarcomas using the time-to-death data. The upper-bound estimate of the cancer risk from 1 ug/m^3 of EDC in air is 7×10^{-6}. The upper-bound estimate of the risk from 1 ug/L of EDC in drinking water is 2×10^{-6}. The cancer risk of EDC by inhalation is calculated by two methods: 1) a direct estimation based on the EDC gavage study, assuming that the absorption rate by inhalation is one-third of that by the oral route; and 2) an indirect estimation from the EDB inhalation study. The potencies calculated from both approaches are practically identical.

The potency index for EDC, defined as $q_1^* \times$ molecular weight, lies in the fourth quartile among the 53 suspect carcinogens evaluated by the Carcinogen Assessment Group.

9.5.5 Conclusions

There is evidence that EDC is a potential human carcinogen. This conclusion is based on: 1) positive findings in one oral rat study and one oral mouse study and supportive evidence in two other mouse studies; 2) a positive mutagenicity response in multiple tests; and 3) demonstrated evidence of the presence of reactive metabolites and covalent binding to DNA.

The estimated carcinogenic potency of EDC places it in the 4th quartile of the 53 suspect carcinogens evaluated by the CAG.

Applying the International Agency for Research on Cancer (IARC) classification scheme, this level of evidence in animals would be considered sufficient for concluding that EDC is a potential human carcinogen with a rank of 2B.

United States
Environmental Protection
Agency

Office of Health and
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Washington DC 20460

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April 1984
External Review Draft

Research and Development

Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride)

Review
Draft

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Part 2 of 2

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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EPA-600/8-84-006A
April 1984
External Review Draft

Health Assessment Document for 1, 2, - Dichloroethane (Ethylene Dichloride)

Part 2 of 2

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PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a "source document" for EPA use. The health assessment document was originally developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulation of ethylene dichloride as a hazardous air pollutant. However, the scope of this document has since been expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses are placed in perspective with observed environmental levels.

The EPA's Office of Health and Environmental Assessment (OHEA) is responsible for the preparation of this health assessment document. The OHEA Environmental Criteria and Assessment Office (ECAO-RTP) had overall responsibility for coordination and direction of the document (Dr. Robert M. Bruce, Project Manager). The chapters addressing physical and chemical properties, sampling and analysis and toxic effects were either rewritten or revised by Syracuse Research Corporation. The pharmacokinetics chapter was written by Dr. I.W.F. Davidson of the Bowman Gray School of Medicine, Wake Forest University. The air quality chapters addressing sources, emissions and ambient concentrations were originally written by Syracuse Research Corporation and revised by Radian Corporation under a contract with the Office of Air Quality Planning and Standards.

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APPENDIX A

COMPARISON AMONG DIFFERENT EXTRAPOLATION MODELS

Four models used for low-dose extrapolation, assuming the independent background, are:

Multistage:

$$P(d) = 1 - \exp\,[-(q_1 d + \ldots + q_k d^k)]$$

where q_i are non-negative parameters;

Probit:

$$P(d) = \int_{-\infty}^{A + B\ln(d)} F(x)\,dx$$

where f(.) is the standard normal probability density function;

Weibull:

$$P(d) = 1 - \exp\,[-bd^k]$$

where b and k are non-negative parameters; and

One-hit:

$$P(d) = 1 - \exp\,[-bd]$$

where b is a non-negative parameter.

The maximum likelihood estimates (MLE) of the parameters in the multistage and one-hit models are calculated by means of the program GLOBAL82, which was developed by Howe and Crump (1982). The MLE estimates of the parameters in the probit and Weibull models are calculated by means of the program RISK81, which was developed by Kovar and Krewski (1981).

Table A-1 presents the MLE of parameters in each of the four models that are applicable to a data set.

TABLE A-1. MAXIMUM LIKELIHOOD ESTIMATES OF THE PARAMETERS FOR EACH OF THE FOUR EXTRAPOLATION MODELS BASED ON DIFFERENT DATA BASES

Data base	Multistage	Probit	Weibull	One-hit
Hemangiosarcomas in male rats, dose with surface correction	$q_1 = 3.65 \times 10^{-2}$ $q2 = 0$	$A = -1.43$ $B = 0.34$	$b = 9.08 \times 10^{-2}$ $k = 0.52$	$b = 3.65 \times 10^{-2}$
Hemangiosarcomas in male rats, dose without surface correction	$q_1 = 7.03 \times 10^{-3}$ $q2 = 0$	$A = -1.99$ $B = 0.34$	$b = 3.84 \times 10^{-2}$ $k = 0.52$	$b = 7.03 \times 10^{-3}$
Hepatocellular carcinomas in male mice, dose with surface correction	$q_1 = 1.03 \times 10^{-2}$ $q_2 = 1.47 \times 10^{-3}$	$A = -2.75$ $B = 0.86$	$b = 8.07 \times 10^{-3}$ $k = 1.49$	$b = 2.32 \times 10^{-2}$
Heptocellular carcinomas in male mice, dose without surface corrections	$q_1 = 8.18 \times 10^{-4}$ $q_2 = 9.25 \times 10^{-6}$	$A = -4.92$ $B = 0.86$	$b = 1.84 \times 10^{-4}$ $k = 1.49$	$b = 3.04 \times 10^{-3}$

APPENDIX B

RISK CALCULATION BASED ON TIME-TO-EVENT DATA

Because of the high mortality rate of rats in the high-dose group of the NCI (1978) gavage study, it is more appropriate to use time-to-event data (Table B-1) to calculate the potency of EDC. The probability of cancer by time t at dose d is given by:

$$P(d,t) = 1 - \exp\,[-f(t) \times g(d)]$$

where g(d) is a polynomial in dose d, and f(t) is a function of time t. The maximum likelihood estimate of the parameters and the asymptotic properties of the incremental risk estimate were investigated by Daffer et al. (1980). Their approach to estimating the parameters resembles Cox's regression-life-table approach (Cox 1972), in which the time function f(t) need not be specified.

Using the data in Table B-1, the lifetime cancer risk is estimated to be

$$q_1^* = 6.9 \times 10^{-2} \text{ mg/kg/day}$$

This value is the 95% upper bound of the risk calculated at t = 90 weeks. Since the model fits the data very well up to 90 weeks but poorly beyond 90 weeks (overestimates), P(d, 90) is used to approximate the lifetime risk. This seems reasonable because the median lifespan for control animals is also less than 90 weeks (approximately 70% of the control animals died before 90 weeks).

TABLE B-1. TIME-TO-DEATH IN WEEKS FROM HEMANGIOSARCOMAS IN MALE OSBORNE-MENDEL RATS FED EDC BY GAVAGE

Control (vehicle and untreated):

28, 37, 50, 50, 53, 53, 53, 54, 57, 57, 57, 57, 57, 61, 61, 69, 71, 76, 78, 80, 80, 83, 85, 86, 87, 89, 90, 101, 101, 104, 106, 106, 106, 106, 106, 108, 110, 110, 110, 110.

Low-dose group:

30, 34, 36, 51, 52, 52, 55, 55, 59, 61, 63, 65, 69, 73(H)[a], 74(H), 75, 75, 76, 77, 77, 77(H), 77, 80, 81, 82, 82, 82, 84, 87(H), 89(H), 89, 89, 89, 90, 92, 92, 93(H), 95(H), 96, 97, 98, 99, 99, 102(H), 103, 103, 104, 104, 109(H), 110.

High-dose group:

3, 8, 9, 9, 10, 10, 10, 10, 10, 11, 15, 15, 16, 20, 22, 33, 33, 33, 34, 37, 41, 48, 51, 52, 54, 57, 58, 59, 60, 61(H), 62, 63, 63, 68(H), 68(H), 71, 72, 73, 74, 74(H), 74, 74, 76(H), 76, 78(H), 83(H), 84, 89, 101.

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[a] H indicates death from hemangiosarcoma.

APPENDIX C

CALCULATION OF EDB CARCINOGENIC POTENCIES BY GAVAGE AND INHALATION ROUTES

The data used for calculating the potency of EDB by gavage are presented in Table C-1. The data from the high-dose group are not used because the dose pattern from the high-dose group was drastically modified during the experiment, resulting in a time-weighted dose almost identical to that of the low-dose group. Using the life-table approach (Kaplan and Meier 1958), the probability of cancer at week 49 (the end of the study) is 0.37 with the 95% one-sided upper-confidence limit at 0.46. Thus, the upper-bound estimate of the slope in the one-hit model, $P = 1 - \exp(-bd)$, is:

$$\begin{aligned} b &= [-\ln (1-P)]/d \\ &= [-\ln (1-0.46]/5.01 \\ &= 0.12 \text{ mg/kg/day.} \end{aligned}$$

The lifetime cancer potency, adjusting for the less-than-lifetime study, is

$$B = 0.12 \times (90/49)^3 = 0.74 \text{ mg/kg/day}$$

where 90 weeks is the lifespan that is also used in the EDC calculation when time-to-event data are used.

Therefore, EDB is approximately 10 times more potent than EDC (i.e., 0.74/0.069).

The data used for calculating the potency of EDB by inhalation are presented in Table C-2. The carcinogenic potency of EDB by inhalation is calculated on the basis of nasal cavity tumors in male rats from the NCI inhalation study on EDB (NCI 1979), using the linearized multistage model. The potency of EDB by inhalation is

$$6.77 \times 10^{-5}/(ug/m^3).$$

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TABLE C-1. TIME-TO-DEATH IN WEEKS FROM HEMANGIOSARCOMAS IN MALE OSBORNE-MENDEL RATS FED EDB BY GAVAGE (NCI 1978)

Low-dose group (38 mg/kg/day)[a]

31(H)[b], 32, 34(H), 34(H), 35, 36, 37, 38(H), 39, 39, 40, 41,
42, 43, 43, 43, 43, 43, 43, 44, 44, 44, 46, 46, 47, 47, 48(H),
48, 48, 48, 48, 49(H), 49(H), 49(H), 49(H), 49(H), 49(H), 49,
49, 49, 49, 49, 49, 49, 49, 49, 49, 49, 49, 49.

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[a] The animals were fed EDB 5 days per week for 47 weeks (out of 49 weeks observation period). The human equivalent dose is (38 mg/kg/day) x (5/7) x (47/49) x $(0.5/70)^{1/3}$ = 5.01 mg/kg/day.

[b] H indicates that the animals died from hemangiosarcomas. It is assumed that all animals observed with tumors at week 49 died from the tumors. This assumption seems reasonable, since the time from exposure to tumor death was very short.

TABLE C-2. INCIDENCE OF NASAL CAVITY TUMORS IN MALE FISCHER 344 RATS ADMINISTERED EDB BY INHALATION (NCI 1979)

Human equivalent dose (ug/m^3)[a]	Animal dose (ppm)	Response
0	0	0/50 (0%)
1.39×10^4	10	39/50 (78%)
5.57×10^4	40	41/50 (82%)

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[a] Human equivalent dose = d x (5/7) x (6/24) = 0.178 x d. The dose is converted to the unit of ug/m^3 by using 1 ppm = 7.83×10^3 ug/m^3.